A randomised, double-blind placebo controlled trial of the clinical and cost effectiveness of low dose oral theophylline as an adjunct to inhaled corticosteroids in preventing exacerbations of chronic obstructive pulmonary disease.

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ABSTRACT

Background: Despite widespread use of therapies such as inhaled corticosteroids (ICS), people with chronic obstructive pulmonary disease (COPD) continue to suffer, have reduced life expectancy and utilise considerable NHS resources. Laboratory investigations have demonstrated that at low plasma concentrations (1-5mg/l) theophylline markedly enhances the anti-inflammatory effects of corticosteroids in COPD.

Objective: To determine the clinical and cost-effectiveness of adding low-dose theophylline to a drug regimen containing ICS in people with COPD at high risk of exacerbation.

Design: A multi-centre pragmatic double-blind randomised placebo controlled clinical trial.

Setting: 121 UK primary and secondary care sites.

Participants: People with COPD ($FEV_1/FVC<0.7$) currently on a drug regimen including ICS with a history of ≥2 exacerbations treated with antibiotics and/or oral corticosteroids in the previous year.

Interventions: Participants were randomised (1:1) to receive either low-dose theophylline or placebo for a year. The dose of theophylline (200mg once or twice a day) was determined by ideal body weight and smoking status.

Primary Outcome: The number of participant reported exacerbations in the one year treatment period treated with antibiotics and/or oral corticosteroids.

Results: 1578 people were randomised, (60% from primary care): 791 theophylline, 787 placebo. There were 11 post-randomisation exclusions. 1567 participants were prescribed study medication: 788 theophylline, 779 placebo. Participants in the trial arms were well balanced; mean (SD) age 68.4 (8.4) years, 54% were male, 32% currently smoked, mean (SD) FEV_1 51.7% (20.0) predicted.

Primary outcome data were available for 98% of participants: 772 theophylline, 764 placebo, there were 1489 person years of follow up data. The mean (SD) number of exacerbations in participants allocated to theophylline was 2.24 (1.99) and for participants allocated to placebo 2.23 (1.97), adjusted incident rate ratio (IRR) (95% CI) 0.99 (0.91, 1.08).

Low-dose theophylline had no significant effects on lung function (FEV_1), incidence of pneumonia, mortality, breathlessness, or measures of quality of life or disease impact. Hospital admissions because of COPD exacerbation were less frequent with low-dose

theophylline, adjusted IRR 0.72 (0.55, 0.94), however, 39 of the excess 51 hospital admissions in the placebo group were accounted for by 10 participants having ≥3 exacerbations.

There were no differences in the reporting of theophylline side effects between the theophylline and placebo arms.

Limitations: A greater than expected number of participants (26%) ceased study medication, this was balanced between theophylline and placebo arms and mitigated by over-recruitment (n=154) and high rate of follow up. The limitation of not using documented exacerbations is addressed by evidence that patient recall is highly reliable and the results of a small within-trial validation study.

Conclusion: For people with COPD at high risk of exacerbation, the addition of low-dose oral theophylline to a drug regimen that includes inhaled corticosteroid, confers no overall clinical or health economic benefit. This result was evident from the intention to treat and per-protocol analyses.

Future work: To promote consideration of the findings of this trial in National and International COPD Guidelines.

Study registration: ISRCTN27066620 registered 19th September 2013.

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(Word count n=500)

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SUPPLEMENTARY MATERIAL

LIST OF ABBREVIATIONS

ABW	Actual body weight
AR	Adverse reaction
ASSET	Low-dose Theophylline as Anti-inflammatory Enhancer in Severe Chronic Obstructive Pulmonary Disease trial
ATS	American Thoracic Society
bd	Twice a day
BMI	Body mass index
BNF	British National Formulary
CAT	COPD Assessment Test
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator, Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRN	Clinical Research Network
CSRI	Client Service Receipt Inventory
Css	Steady state concentration
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
ECSC	European Coal and Steel Community
EQ-5D-3L	EuroQoL, 5 dimension, 3 level
ERS	European Respiratory Society

FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GBP	£ sterling
GLM	Generalised linear model
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practice, General Practitioner
HARQ	Hull Airways Reflux Questionnaire
HDAC	Histone deacetylase
HR	Hazard ratio
IBW	Ideal body weight
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
IL-8	Interleukin-8
IQR	Inter quartile range
IRR	Incident rate ratio
ISD	Information Services Division
ITT	Intention to treat
LABA	Long acting β2 agonist
LAMA	Long acting muscarinic antagonist
MHRA	Medicines and Healthcare products Regulatory Agency
MICE	Multiple imputation using chained links
MMP-9	Matrix metallo proteinase 9
mMRC	modified Medical Research Council
MR	Modified release

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR HTA	National Institute for Health Research Health Technology Assessment
OCS	Oral corticosteroid
Od	once daily
OR	Odds ratio
PDE	Phosphodiesterase
PIC	Participant identification centre
PI3K	phosphoinositide-3-kinase
PIL	Participant information leaflet
PPI	Patient and Public Involvement
PPSRU	Personal Social Services Research Unit
PSS	Personal Social Services
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
REC	Research Ethics Committee
RR	Relative risk
SABA	Short acting β2 agonist
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics
SVC	Slow vital capacity

THIN	The Health Improvement Network
TSC	Trial Steering Committee
TWICS	Theophylline with Inhaled Corticosteroids
UK	United Kingdom
VAS	Visual analogue scale

PLAIN ENGLISH SUMMARY

Chronic obstructive pulmonary disease (COPD) is a long term lung disease that cannot be cured. The main symptom is shortness of breath on exertion. In the UK about 1.2 million people have COPD. It is a major cause of death and costs the NHS more than £1 billion a year. Sudden "flare ups" of symptoms often need emergency treatment, they shorten life expectancy and reduce peoples' ability to get on with their lives.

Theophylline is a drug that has been around for decades. It used to be used in high doses to treat COPD by opening up airways. However, its benefits were limited and it often caused unpleasant side effects. High-dose theophylline has been replaced by inhalers such as inhaled corticosteroids (ICS). Recent work in the laboratory and in animal models suggests that at low-dose, theophylline could make ICS work better in COPD with none of the side effects of high dose theophylline.

The TWICS trial tested whether adding low-dose theophylline reduces flare ups in people with COPD taking ICS. 1578 people with COPD from 121 centres all over the UK took part. Participants were randomly divided into two groups: one took low dose theophylline and the other took dummy placebo pills. Participants were asked to attend visits at 6 and 12 months.

791 participants were prescribed low-dose theophylline and 787 were prescribed dummy placebo pills. Although not everyone took the tablets for a whole year we were able to count the number of flare ups in 98% of those taking part. In total there were 3430 flare ups. On average the people taking low-dose theophylline had 2.24 flare ups and the people taking placebo had 2.23 flare ups.

Overall the trial shows that for people with COPD, taking low-dose theophylline on top of steroid inhalers makes no real difference.

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SCIENTIFIC SUMMARY

Background

Chronic obstructive pulmonary disease (COPD) is an incurable lung disease characterised by airway inflammation and progressive airflow limitation, typical symptoms include slowly worsening shortness of breath on exertion, productive cough and wheeze. The progressive airflow limitation of COPD is associated with increasing symptoms, ill health, work absence, disability and premature mortality. In the UK there are 1.2 million people with diagnosed COPD, it is the fifth leading cause of death, it is also a leading cause of emergency hospital admission and costs the NHS in excess of £1billion/year.

Acute deteriorations in symptoms known as exacerbations are an important clinical feature of COPD, many require treatment with antibiotics and/or corticosteroids and the severest require hospital admission. Exacerbations are associated with increased ill health, a poorer prognosis and are the most costly aspect of COPD for the NHS. Recent studies have identified a frequent COPD exacerbator phenotype defined as ≥2 exacerbations in a year. Such patients can be reliably identified by patient recall and are highly likely to exacerbate in subsequent years. Despite advances in management, there is still an unmet need for improved pharmacological treatment of COPD particularly the prevention of exacerbations.

Oral theophylline has been used in the treatment of COPD for over 70 years. Conventionally theophylline has been used as a bronchodilator, however in order to achieve modest clinical effects relatively high blood concentrations (10-20mg/l) are required that are also associated with a wide range of well recognised side effects. The availability of more effective inhaled therapies, theophylline's narrow therapeutic index, its modest clinical effect, and side effect profile has resulted in current COPD guidelines relegating high-dose theophylline to third line therapy although in low to middle income countries it is often used earlier in clinical practice.

In recent years molecular mechanisms contributing to the reduced corticosteroid sensitivity of the airway inflammation of COPD have been elucidated. *In vitro* and animal models have demonstrated that at low plasma concentrations (1-5mg/l) there is a marked synergistic effect between theophylline and corticosteroids, with theophylline inducing a 100-10,000 fold increase in the suppressive effect of corticosteroids on the release of pro-inflammatory

mediators. A number of small exploratory studies of short duration have confirmed that at low-dose, theophylline increases the anti-inflammatory properties of inhaled corticosteroids (ICS) as evidenced by molecular signatures. Two small year-long hospital based placebo controlled trials of low-dose theophylline in COPD have reported conflicting results. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) management strategy guideline highlights that the clinical relevance of low-dose theophylline has not been fully established and that clinical evidence on low-dose theophylline, particularly on exacerbations, is limited and contradictory.

The theophylline with inhaled corticosteroids (TWICS) trial was a pragmatic double blind randomised, placebo-controlled clinical trial built on emerging evidence that low-dose (plasma concentration 1-5mg/l) theophylline may produce a beneficial synergistic effect in COPD by increasing the corticosteroid sensitivity of the airway inflammation underlying COPD and as a consequence reduce the rate of COPD exacerbation when used in conjunction with ICS.

Objectives

The primary objective was to determine the clinical and cost-effectiveness of adding low-dose theophylline to ICS therapy in patients with COPD and a history of two or more exacerbations treated with antibiotic and/or oral corticosteroids in the previous year, the primary clinical outcome being the number of exacerbations in the one year treatment period requiring treatment with antibiotics and/or oral corticosteroids. The primary economic outcome was cost-per-QALY gained during the one year treatment period.

The secondary objectives were to compare the following outcomes between participants treated with low-dose theophylline and those treated with placebo:

- Hospital admissions with a primary diagnosis of exacerbation of COPD
- Total number of episodes of pneumonia
- Total number of emergency hospital admissions
- Lung function
- All-cause and respiratory mortality
- Drug reactions and serious adverse events
- Health related quality of life

- Disease specific health status
- Total inhaled corticosteroid dose/usage
- Health care utilisation
- Modelled lifetime incremental cost per Quality Adjusted Life Year
- Time to first exacerbation (an additional secondary objective)

Methods

TWICS was a pragmatic double-blind randomised, placebo-controlled, UK multicentre clinical trial that compared the addition of low-dose theophylline or placebo for 52 weeks to current COPD therapy that included ICS, in patients with COPD who had had ≥2 exacerbations in the previous year treated with oral corticosteroids and/or antibiotics. The aim was to recruit 1,424 participants with at least 50% being recruited from primary care.

Inclusion criteria

Participants were people with COPD likely to exacerbate during the 52 week treatment period. The key inclusion criteria were:

- Aged ≥ 40 years
- Smoking history of >10 pack years
- Predominant respiratory diagnosis of COPD ($FEV_1/FVC<0.7$)
- Current use of ICS therapy
- Patient report of ≥2 exacerbations treated with antibiotics and/or oral corticosteroids in the previous year

Exclusion criteria

The key exclusion criteria are listed below, they include concomitant treatment with drugs with the potential to increase plasma theophylline concentration above the low-dose range of 1-5mg/l.

- Severe or unstable ischaemic heart disease
- A predominant respiratory disease other than COPD including alpha-1-antitrypsin deficiency
- Current use of drugs with the potential to increase plasma theophylline

Participant identification & recruitment

Participants were identified and recruited from both primary and secondary care sites across the UK. Recruitment strategies differed between centres depending on local geographic and NHS organisational factors.

Randomisation/treatment allocation

Participants were randomised using an internet based computerised randomisation system created and administered by the Centre for Healthcare Randomised Trials (CHaRT), University of Aberdeen. Participants were stratified by trial centre/area and recruitment setting (primary and secondary) and then randomised with equal probability to the intervention (low-dose theophylline) and control (placebo) arms.

Intervention

The treatment period was 52 weeks with either Uniphyllin MR 200 mg tablets or a visually identical placebo. Dosing was based upon pharmacokinetic modelling incorporating the major determinants of theophylline steady state concentration, designed to achieve a steady state plasma theophylline of 1-5 mg/l. The dosing of both active and placebo was determined by the participant's ideal body weight (IBW) and smoking status.

- Uniphyllin MR 200 mg once daily (or one placebo once daily) for non-smoking participants, or participants who smoked but had IBW ≤ 60kg
- Uniphyllin MR 200 mg twice daily (or one placebo twice daily) for participants who smoked with IBW > 60 kg

All supplies of study tablets were delivered to the participants' homes except for participants recruited in secondary care sites who received their initial 4-week supply from their local Clinical Trials Pharmacy.

Data collection

Outcome data were collected by face to face assessments conducted at recruitment/baseline (week 0), 6 months (week 26) and 12 months (week 52). Participants unable to attend the 6 and 12 month assessments were followed up by telephone, home visit, or sent the questionnaires to complete at home. The key data collected were:

- Number of COPD exacerbations requiring antibiotics/oral corticosteroids (i.e. moderate/severe exacerbations)

- Number of unscheduled hospital admissions
- Health related quality of life (EQ-5D-3L)
- Disease related health status (COPD Assessment Test (CAT))
- Modified MRC dyspnoea score
- Post bronchodilator spirometry (FEV_1, FVC)
- Health care utilisation
- Adverse reactions and serious adverse events
- Adherence, persistence with study medication

Sample Size

Sample size was based on the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study that indicated for our study population, the mean (SD) number of COPD exacerbations within 1 year would be 2.22 (1.86). An estimated 669 subjects were needed in each trial arm to detect a 15% reduction in COPD exacerbations (i.e., from a mean of 2.22 to 1.89) with 90% power at the 5% significance level. Allowing for 6% loss to follow-up this was inflated to 712 participants in each study arm, giving 1424 in total.

Statistical analysis

All analyses were pre-specified in the statistical and health economic analysis plan approved in advance of analysis. All analyses were according to the intention to treat (ITT) principle with a per-protocol analysis performed as a sensitivity analysis. The per-protocol analysis excluded participants who were not compliant, with compliance being defined as taking ≥70% of their expected doses of study medication.

Results

Recruitment to the study took place between 6th February 2014 and 31st August 2016, a total of 1578 people were randomised: 791 theophylline, 787 placebo. Participants were recruited in 121 study sites (88 primary care, 33 secondary care), 941 (60%) of participants were identified in primary care. There were 11 post-randomisation exclusions (3 theophylline, 8 placebo), 1567 participants were prescribed study medication: 788 theophylline, 779 placebo. A higher proportion (26%) of participants than the expected 6% ceased their study medication, to counteract this, recruitment continued beyond 1424 in the time available with the total number recruited being 1578.

The baseline characteristics of the participants allocated to theophylline and placebo were balanced: mean (SD) age 68.4 (8.4) years, 54% male, mean BMI 27.2 (6.1) kg/m^2, 31.7% currently smoked, 80% were using inhaled corticosteroids/long-acting-beta2-agonists/long-acting muscarinic antagonists, mean FEV_1 51.7 (20.0)% predicted, 13.6% had very severe airflow obstruction (FEV_1<30% predicted), 37.7% severe (FEV_1 30-50% predicted), 39.6% moderate (FEV_1 50-80% predicted) and 9.2% mild airflow obstruction (FEV_1>80% predicted). The mean (SD) number of participant reported exacerbations in previous year was 3.6 (2.2). CAT scores indicated that COPD had a high impact on participants' lives, mean 22.6 (7.7), mean EQ-5D-3L utility score was 0.63 (0.28).

Intention to treat analysis

Primary outcomes

For the ITT analysis primary outcome data were available for 98% of participants: 772 theophylline, 764 placebo, there were 1489 person years of follow up data. In total there were 3430 exacerbations, 1727 theophylline, 1703 placebo, the mean (SD) number of exacerbations in participants allocated to theophylline was 2.24 (1.99) and for participants allocated to placebo 2.23 (1.97), unadjusted incident rate ratio (95% CI) 1.00 (0.92, 1.09), adjusted IRR 0.99 (0.91, 1.08).

Owing to no statistically significant difference in exacerbation rate between treatment arms, the economic analysis was limited to a within trial analysis. There was a significant difference in unadjusted mean total costs, higher in the placebo arm compared to theophylline arm £452 (95%CI £133, £771). This was driven by a significant difference in exacerbation costs between arms of £447 (95% CI £186, £709). This difference was a result of higher costs in the placebo arm for hospitalisations. After adjusting mean costs for baseline characteristics there was no significant difference between arms in either exacerbation or total costs; the difference in total costs was £222 (95% CI -£27, £472), higher in the placebo arm.

Adjusted mean quality adjusted life-years were 0.621 (SE 0.006) in the theophylline arm and 0.616 (SE 0.007) in the placebo arm, there was no significant difference between arms. Overall theophylline dominates placebo, with lower costs and higher QALYs. However, this result is not significant and care should be taken when interpreting it.

Secondary outcomes

There were 319 severe COPD exacerbations treated in hospital: 134 theophylline, 185 placebo. The mean number of severe COPD exacerbations treated in hospital was: 0.17 (0.49) theophylline, 0.24 (0.66) placebo, unadjusted IRR 0.72 (0.55, 0.95), adjusted IRR 0.72 (0.55, 0.94). However, 39 of the excess 51 hospital admissions in the placebo group were accounted for by 10 participants having ≥3 exacerbations. Low-dose theophylline had no significant effect on: non-COPD related hospital admissions, adjusted IRR 0.99 (0.71, 1.38); episodes of pneumonia, incidence 1.5%, unadjusted IRR 1.55 (0.67, 3.62); FEV_1 % predicted, adjusted mean difference (95% CI) difference -0.56 (-2.42, 1.30); CAT score, adjusted marginal mean difference 0.01 (-0.65, 0.68); mMRC breathlessness score, adjusted OR 1.20 (0.88, 1.63); total mortality 2.5% theophylline, 1.8% placebo, p=0.400; COPD/respiratory related mortality 0.9% theophylline, 1.1% placebo, p=0.762.

Low-dose theophylline was not associated with a significant increase in adverse reactions (ARs) or serious adverse events (SAEs): proportion of participants reporting ARs 48.1% theophylline, 43.9% placebo p=0.116, total number of ARs 883 theophylline, 818 placebo, proportion of participants reporting SAEs: 13.2% theophylline, 14.0% placebo, p=0.616. There were no differences in the profiles of ARs or SAEs events between the theophylline and placebo arms.

Per-protocol analysis

Primary outcome

Of the 1578 participants randomised, 1567 were prescribed study medication, primary outcome data were missing for 31: 16 theophylline, 15 placebo. Adherence/compliance was <70% for 356 participants: 181 (23.4%) theophylline, 175 (22.9%) placebo, p=0.802. The reasons given by participants for ceasing study medication were equally distributed between the theophylline and placebo arms.

For the per-protocol analysis primary outcome data were available for 1180 (75%) of participants: 591 theophylline, 589 placebo, there were 1146 person years of follow up data. There were 2556 exacerbations: 1298 theophylline, 1258 placebo, the mean number of exacerbations in participants allocated to theophylline was 2.20 (1.96) and for participants allocated to placebo 2.14 (1.92), unadjusted IRR 1.02 (0.92, 1.13), adjusted IRR 1.00 (0.91, 1.10).

Secondary outcomes

There were 218 severe COPD exacerbations treated in hospital: 92 theophylline, 126 placebo. The mean number of severe COPD exacerbations treated in hospital was: 0.16 (0.45) theophylline, 0.21 (0.61), adjusted IRR 0.70 (0.50, 0.97). For the other secondary outcomes the per-protocol analysis essentially did not differ from the results of the ITT analysis.

Conclusions

This is the first pragmatic double blind randomised placebo controlled trial to assess the effectiveness of adding low-dose theophylline to a drug regimen containing ICS in people with COPD at high risk of exacerbation, the analyses demonstrated that overall, low-dose theophylline has no clinical or health economic benefit.

Implications for healthcare

This study is the largest trial of low-dose theophylline in COPD to date. National and International COPD Guidelines will need consider the findings of this study when making recommendations on the treatment of COPD and the prevention of COPD exacerbations.

Recommendations for research

A further study investigating the clinical and cost-effectiveness of low-dose theophylline in reducing severe COPD exacerbations requiring admission to hospital needs careful consideration. Such a study would necessarily be very large.

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Study registration

ISRCTN27066620 registered 19th September 2013.

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CHAPTER 1 - INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as "a common preventable and treatable disease characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients".[1] People with COPD typically present with breathlessness on exertion, a productive cough and wheeze. COPD is usually diagnosed from the age of 40 onwards and prevalence increases with age.[2] In westernised countries COPD is predominantly (80-90%) caused by cigarette smoking,[3] but outdoor air pollution and occupational exposure to dusts, vapours and fumes can be significant contributory factors.[4, 5] COPD is closely associated with social deprivation, and makes a major contribution to health inequalities in the UK.[6] The progressive airflow limitation of COPD is associated with increasing disability, work absence, long-term morbidity, common physical and psychological co-morbidities, and premature mortality. People with COPD are more likely to have associated comorbidities,[7] including ischaemic heart disease,[8] hypertension,[9] heart failure,[10, 11] diabetes,[12] osteoporosis,[13] depression[14] and lung cancer,[15] which increase morbidity and complicate its management.[7]

Acute deteriorations in symptoms known as exacerbations are an important clinical feature of COPD. These are usually precipitated by viral/bacterial infection and/or air pollution and are characterised by increasing breathlessness, and/or cough, sputum expectoration and malaise. Many exacerbations are severe enough for patients to seek medical help, usually in the form of antibiotics and/or corticosteroids from their General Practitioner (GP); more severe exacerbations frequently require admission to hospital for more intensive treatment. Exacerbations are associated with accelerated rate of lung function decline,[16] reduced physical activity,[17] reduced quality of life (QoL),[18] increased mortality[19] and increased risk of comorbidities such as acute myocardial infarction and stroke.[20]

The observational Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints study (ECLIPSE) of 2138 COPD patients shed light on factors that influence COPD exacerbations.[21] This study identified a frequent exacerbator phenotype defined as two or more exacerbations in a year that affects about 25% of COPD patients. Patients with this phenotype have an 84% chance of at least one exacerbation in the subsequent year, moreover

this frequent exacerbator phenotype is stable for at least 3 years and can be reliably identified by patient recall. This has been supported by further work demonstrating that the strongest predictor for exacerbations is the number exacerbations in the preceding year.[22] Frequent exacerbators incur a disproportionate amount of the annual National Health Service (NHS) spend on COPD.

The burden of COPD on individuals and the NHS

COPD is a major personal and public health burden.[23, 24] Data from 591 UK general practice (GP) surgeries comprising The Health Improvement Network (THIN) indicate that the prevalence of diagnosed COPD in the UK has increased from about 991,000 in 2004 to 1.2 million in 2012.[2] COPD is the fifth leading cause of death in the UK, accounting for about 5% of all deaths (~30,000 deaths in 2014). More than 80% of COPD patients, irrespective of severity, report a reduced quality of life.[24-26] Co-morbidities are an important feature of COPD, contributing to ill-health and treatment burden. It has been estimated that in the UK 33% of people with COPD have hypertension, 19% have ischaemic heart disease, 18% have depression, 11% have diabetes and 6% have heart failure.[23] Over 50% of people currently diagnosed with COPD in the UK are under 65 years of age and 24 million working days are lost each year from COPD with £3.8 billion/year being lost through reduced productivity.[23]

COPD costs the NHS more than £1 billion/year; for each COPD patient in 2001, average annual NHS direct costs were £819 (>£1,300 in severe COPD), with 60% of this accounted for by exacerbations and 19% due to drug costs.[27] UK hospital episode statistics show that emergency hospital admissions for exacerbations of COPD have steadily increased as a percentage of all admissions from 0.5% in 1991 to 1% in 2000 and to 1.5% in 2008/9.[28] In 2008/9, COPD exacerbations resulted in 164,000 hospital admissions in the UK with an average length of stay of 7.8 days, accounting for 1.3 million bed days.[28] COPD is the second leading cause of emergency admission to hospital in the UK and is one of the most costly inpatient conditions treated by the NHS.[23, 24] At least 10% of emergency admissions to hospital are as a consequence of COPD and this proportion is even greater during the winter. Approximately 25% of patients who have been diagnosed as having COPD are admitted to hospital at some point and about 15% of COPD patients are admitted each year.[23, 24] Over 30% of patients admitted to hospital with an exacerbation of COPD are readmitted within 30 days and an average of 12% of COPD patients die in the year following admission to hospital.[19]

Despite advances in management that have led to the current National Institute for Health and Care Excellence (NICE) COPD guidelines, there is still an unmet need for improved pharmacological treatment of COPD particularly the prevention of exacerbations.

Standard COPD therapy

Standard COPD therapy remains suboptimal. At the time the Theophylline With Inhaled Corticosteroids study (TWICS) was conceived most international COPD management guidelines recommended the use of inhaled corticosteroids (ICS) usually in combination with inhaled long acting β_2 agonists (LABA) known as ICS-LABA to reduce COPD exacerbation rates and to improve lung function and quality of life.[1, 24] Although more recent guidelines advocate the use of LABA in combination with long acting muscarinic antagonists (LAMA), ICS-LABA and ICS/LABA/LAMA combinations remain major therapeutic options and continue to be used very widely in the treatment of COPD.[29, 30] However, when compared to the marked responses observed in asthma, ICS in COPD fail to fully suppress airway inflammation and patients continue to have exacerbations despite high ICS doses. Furthermore little or no positive impact of ICS on mortality or disease progression is evident[31, 32] and concerns have been raised about long term sequelae of high dose ICS use in COPD.[33, 34] A relative insensitivity of COPD airway inflammation to the anti-inflammatory effects of high dose ICS has been demonstrated in induced sputum and airway biopsies of people with COPD.[35-37]

In recent years molecular mechanisms contributing to the reduced corticosteroid sensitivity of COPD have been elucidated. The chronic airway inflammation of COPD is driven by expression of multiple inflammatory genes regulated by acetylation of core histones which open up the chromatin structure enabling transcription factors and RNA polymerase II to bind to DNA, enabling gene transcription and increased synthesis of inflammatory proteins.[38] In COPD there is increased acetylation of core histones associated with the promoter regions of inflammatory genes, with the degree of acetylation being positively associated with disease severity.[39] Histone acetylation is reversed by histone deacetylase (HDAC) enzymes. Corticosteroids appear to work by reversing histone acetylation through the recruitment of a specific histone deacetylase called HDAC2,[38, 40, 41] thereby switching off activated inflammatory genes. In people with COPD increased histone acetylation appears to be a consequence of markedly reduced HDAC2 activity/expression in airways, lung tissue and

alveolar macrophages.[39] It has been shown that the oxidative stress of COPD activates the enzyme phosphoinositide-3-kinase (PI3K)-δ, which then phosphorylates downstream kinases resulting in the phosphorylation and inactivation of HDAC2.[41, 42] The critical role played by reduced HDAC2 in the corticosteroid resistance of COPD is demonstrated by the finding that the corticosteroid resistance of COPD bronchoalveolar macrophages is completely reversed by overexpressing HDAC2 (using a plasmid vector) to levels seen in non-COPD controls.[40]

Low-dose theophylline may have synergistic anti-inflammatory effects with corticosteroids

Oral theophylline has been used in the treatment of COPD for over 70 years but usually at doses required to achieve relatively high blood concentrations (10-20mg/l). It has been observed that the reduced HDAC2 activity of COPD can be reversed in a dose-dependent manner by low-doses of theophylline, moreover low-dose theophylline reduces corticosteroid insensitivity in COPD such that there is a marked synergistic interaction between theophylline and corticosteroids in suppressing the release of inflammatory mediators from alveolar macrophages from COPD patients. This *in vitro* work has shown that at (low) concentrations of 1-5mg/l theophylline increases HDAC2 activity (6 fold) but at (high) concentrations over about 10 mg/l theophylline inhibits rather than stimulates HDAC2 activity.[43, 44] These studies show that at concentrations of 1-5mg/l there is a marked synergistic effect between theophylline and corticosteroids, with theophylline inducing a 100-10,000 fold increase in the suppressive effect of corticosteroids on the release of pro-inflammatory mediators. Such an increase in corticosteroid potency is worthy of clinical interest particularly if associated with reduced exacerbation rate. An explanation for the ability of low-dose (1-5mg/l) theophylline to increase HDAC activity has been described: it specifically inhibits the enzyme PI3K-δ with consequent restoration of HDAC2 activity to normal in COPD macrophages, rendering them steroid responsive. In cigarette smoke exposed mice,[42] steroid-resistant lung inflammation has also been found to be reduced by low-dose theophylline when given together with steroids. Similarly rats exposed to cigarette smoke were found to have markedly decreased lung HDAC2 expression and that reduced HDAC2 expression was correlated with increased lung destruction index.[45] The increased lung destruction index was restored to normal with ICS treatment in combination with low, (but not high), dose theophylline. It was concluded that low-dose theophylline might provide

protection from cigarette smoke damage and improve the anti-inflammatory effects of steroids by increasing HDAC2 activity.

In human peripheral blood mononuclear cells corticosteroid insensitivity and reduced HDAC2 activity after oxidative stress have been shown to be reversed with low concentrations of theophylline.[46] In a study of human alveolar macrophages extracted from resected lung samples, the addition of hydrogen peroxide reduced HDAC expression and was associated with an increase in interleukin-8 (IL-8) and matrix metallo proteinase 9 (MMP-9) release.[47] The addition of low-dose theophylline restored HDAC expression to levels above that observed with LABA, ISC and ICS/LABA.

These basic research studies suggest that low-dose (1-5mg/l) theophylline could increase HDAC activity and hence reduce corticosteroid resistance in COPD patients thereby enabling ICS to switch off inflammation and potentially more effectively reduce exacerbation rates. This is supported by findings from two small randomised controlled trials (RCT) and a population based health administration database study. The first RCT in 35 patients with acute COPD exacerbations found that low-dose theophylline increased responsiveness to corticosteroids as measured by increased HDAC activity and further reduced concentrations of pro-inflammatory mediators in induced sputum compared to inhaled corticosteroids alone.[48] In the second small (n=30) pilot RCT of COPD patients, the combination of low-dose theophylline with high dose ICS was associated with increased HDAC activity, improved lung function and reduced sputum inflammatory cells and mediators, whereas either drug alone was ineffective.[49] A Canadian health administration database study of 36,492 COPD patients reported that treatment with theophylline either alone or in combination with ICS was more protective against exacerbations than treatment with LABA or ICS-LABA (relative risk (RR) 0.89, 95% confidence interval (CI) 0.87-0.92).[50]

More recent studies however, have not replicated the results of earlier studies. Fexer et al used data from a German ambulatory COPD management program and closely matched 1496 COPD patients commenced on theophylline with 1496 COPD patients not commenced on theophylline.[51] The use of theophylline was associated with an increased likelihood of exacerbation (hazard ratio (HR) 1.41; 95% CI 1.24-1.60), and hospital admission (HR 1.61; 95% CI 1.29-2.01). Although it was concluded that theophylline is associated with an increased incidence of exacerbations and hospitalisations, it should be noted that this study

did not identify those patients on low-dose theophylline.[51] The Spanish Low-dose Theophylline as Anti-inflammatory Enhancer in Severe Chronic Obstructive Pulmonary Disease (ASSET) trial recruited patients with COPD whilst hospitalised for a COPD exacerbation and randomised to low-dose theophylline (100mg twice a day) or matched placebo in addition to usual ICS/LABA treatment.[52] In total 70 patients were randomised (36 theophylline, 34 placebo) and 46 completed the year of treatment (23 theophylline, 23 placebo). The addition of theophylline had no effect on COPD exacerbation rate nor plasma/sputum concentrations of HDAC and inflammatory mediators. It should be noted that the study was small and designed to detect a 50% reduction in exacerbations.

Conventionally oral theophylline has been used as a bronchodilator in COPD, however in order to achieve modest clinical effects relatively high blood concentrations (10-20mg/l) are required. The bronchodilator effect of high-dose theophylline is the consequence of inhibition of phosphodiesterase (PDE) and consequent relaxation of airway smooth muscle. However non-specific inhibition of PDE by theophylline is also associated with a wide range of well recognised side effects that may occur within the conventional therapeutic range of plasma theophylline: namely nausea, gastro-intestinal upset, headaches, insomnia, seizures, cardiac arrhythmias and malaise. Theophylline toxicity is dose related and this is an issue with conventional theophylline use because the therapeutic ratio of theophylline is small and most of the beneficial bronchodilator effect occurs when near toxic doses are given.[53] Theophylline is metabolised by cytochrome P450 mixed function oxidases and as a consequence theophylline use is further complicated by significant drug interactions with drugs commonly prescribed to people with COPD, e.g. clarithromycin, ciprofloxacin.[54] The narrow therapeutic index, modest clinical effect, side effect profile, drug interactions, the need for blood concentration monitoring and the availability of more effective inhaled therapies has resulted in current COPD guidelines relegating high-dose theophylline to third line therapy.[1]

The TWICS trial was a pragmatic double blind randomised, placebo-controlled clinical trial that was built on emerging evidence that low-dose (1-5mg/l) theophylline may produce a beneficial synergistic effect in COPD by increasing the corticosteroid sensitivity of the airway inflammation underlying COPD and as a consequence reduce the rate of COPD exacerbation when used in conjunction with ICS.

Hypothesis

The hypothesis being tested was that the addition of low-dose theophylline to ICS therapy in COPD reduces the risk of COPD exacerbation requiring treatment with antibiotics and/or oral corticosteroid (OCS) during the year of treatment, delivers quality of life improvements and is cost-effective.

Objectives

The primary objective of the trial was to determine the clinical and cost-effectiveness of adding low-dose theophylline to inhaled corticosteroid therapy in patients with COPD and a history of two or more exacerbations treated with antibiotic and/or oral corticosteroids in the previous year in relation to the number of exacerbations in the one year treatment period requiring therapy with antibiotics and/or oral corticosteroids.

The secondary objectives were to compare the following outcomes between participants treated with low-dose theophylline and those treated with placebo:

- Hospital admissions with a primary diagnosis of exacerbation of COPD
- Total number of episodes of pneumonia
- Total number of emergency hospital admissions
- Lung function
- All-cause and respiratory mortality
- Drug reactions and serious adverse events
- Health related quality of life
- Disease specific health status
- Total inhaled corticosteroid dose/usage
- Health care utilisation
- Incremental cost-per-exacerbation avoided
- Lifetime cost-effectiveness based on extrapolation modelling
- Modelled lifetime incremental cost per Quality Adjusted Life Year (QALY)

An additional secondary objective was:

- Time to first exacerbation of COPD

Outcomes

Primary Outcomes

The primary outcome was the total number of exacerbations of COPD necessitating changes in management (minimum management change - use of oral corticosteroids and/or antibiotics) during the one year treatment period, as reported by the participant.

The primary economic outcome was cost-per-QALY gained during the one year treatment period.

Secondary Outcomes

- Total number of COPD exacerbations requiring hospital admission
- Total number of episodes of pneumonia
- Total number of emergency hospital admissions (all causes)
- Lung function (forced expiratory volume in 1 second ($FEV_{1)}$, forced vital capacity (FVC)) post bronchodilator using spirometry performed to American Thoracic Society/European Respiratory Society (ATS/ERS) standards
- All-cause and respiratory mortality
- Serious adverse events, adverse reactions
- Total dose of inhaled corticosteroid
- Utilisation of primary or secondary health care for respiratory events
- Disease specific health status using the COPD Assessment Test (CAT); modified Medical Research Council (mMRC) dyspnoea scale
- Generic health related quality of life using EuroQoL 5 dimension, 3 level (EQ-5D-3L) Index
- Modelled lifetime incremental cost per Quality Adjusted Life Year.

An additional secondary outcome was:

- Time to first exacerbation of COPD

Role of the funder

The study was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme. The NIHR had input into the trial design through peer review of the proposal but did not have a role in data collection, data analysis, data

interpretation or the writing of the final report. The corresponding author had access to all the data and was responsible for the decision to submit.

CHAPTER 2 - METHODS/DESIGN

Trial design

The study protocol has been published in an open access journal.[55]

TWICS was a pragmatic double blind randomised, placebo-controlled, parallel-arm, UK multicentre clinical trial that compared the addition of low-dose theophylline or placebo for 52 weeks to current COPD therapy that included ICS, in patients with COPD who had had two or more exacerbations of COPD in the previous year treated with oral corticosteroids and/or antibiotics. The aim was to recruit 1,424 participants with at least 50% being recruited in primary care. The trial was approved by Scotland A Research Ethics Committee (REC) (ref 13/SS/0081) and the Medicines and Healthcare products Regulatory Agency (MHRA) (EudraCT 2013-001490-25, CTA 21583/0218/001). All participants provided written informed consent, this included consent to inform the participant's General Practitioner (GP) of involvement and consent to pass on participant's name and address to a third party distributer who delivered the study drug to the participant's home. *Figure 1* provides a schematic representation of study design and schedule. Face-to-face study assessments were carried out on participants at recruitment/baseline, 6, and 12 months as shown in *Figure 2*. The study was registered on 19 September 2013: ISRCTN27066620.

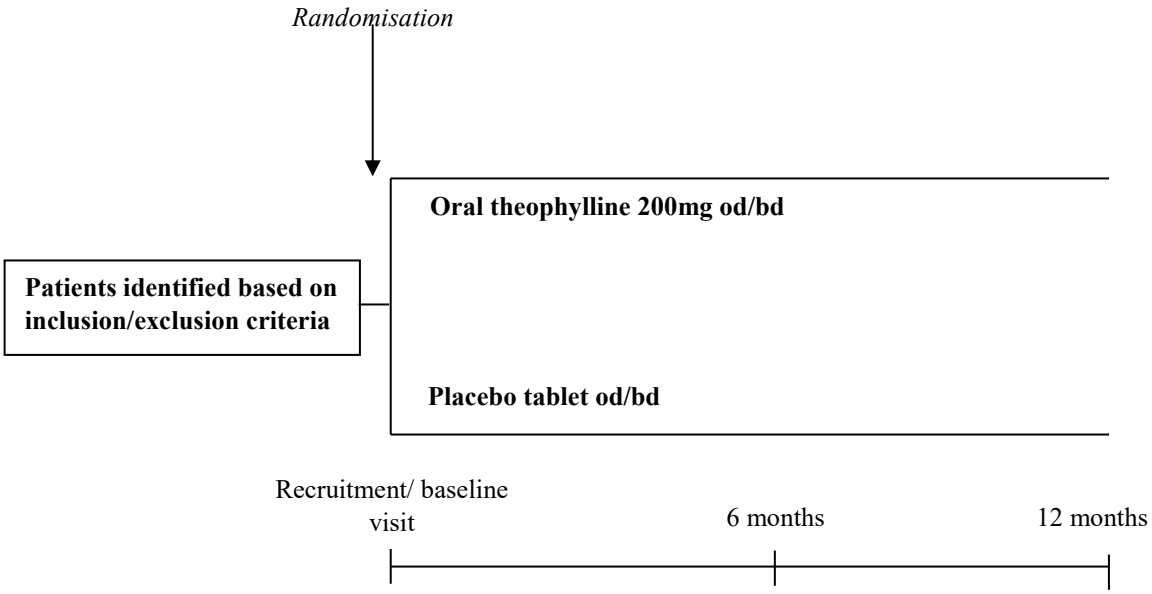
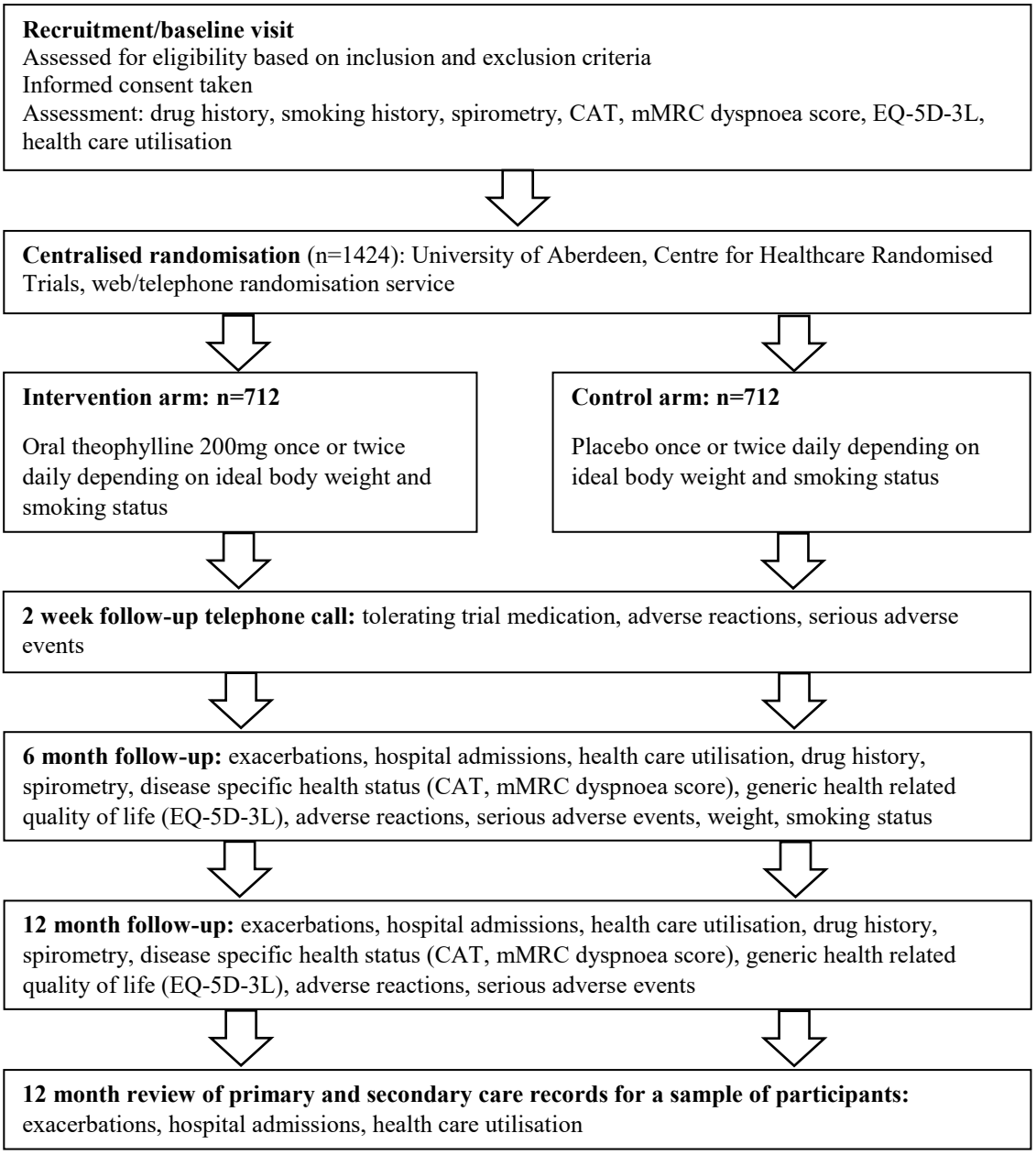


Figure 1: Study design



CAT COPD Assessment Test; mMRC modified Medical Research Council dyspnoea scale;

EQ-5D-3L EuroQoL 5 dimensions, 3 level

Figure 2: Flow diagram of study schedule

Participants

Inclusion criteria

The participants in TWICS were people with COPD likely to exacerbate during the 52 week treatment period as evidenced by two or more exacerbations of COPD in the previous year treated with oral corticosteroids or antibiotics. Participants had to meet all the following inclusion criteria that are typical of studies in people with COPD with exacerbations as the primary endpoint:

- Aged ≥ 40 years
- A smoking history of at least 10 pack years
- An established predominant respiratory diagnosis of COPD (GOLD/NICE Guideline definition: post bronchodilator $FEV_1/FVC<0.7$)[1,2]
- Current use of ICS therapy at the baseline/ recruitment visit
- A history of at least two exacerbations requiring treatment with antibiotics and/or oral corticosteroid use in the previous year, based on patient report
- Clinically stable with no COPD exacerbation for at least 4 weeks
- Able to swallow study medication
- Able and willing to give informed consent to participate
- Able and willing to participate in the study procedures; undergo spirometric assessment, complete study questionnaire

Potential participants with COPD who did not fulfil the lung function criterion of $FEV_1/FVC<0.7$ at the recruitment/baseline visit were asked to complete a slow vital capacity (SVC) manoeuvre and $FEV_1/SVC<0.7$ was accepted as evidence of airflow obstruction. Historical evidence of $FEV_1/FVC<0.7$ was deemed acceptable for those participants who did not achieve $FEV_1/FVC<0.7$ or $FEV_1/SVC<0.7$ or who were unable to complete spirometry at the recruitment/baseline assessment. Eligibility for inclusion was confirmed by a medically qualified person.

Exclusion criteria

The exclusion criteria for TWICS were typical of studies in people with COPD but also included criteria specific for theophylline, notably concomitant treatment with drugs that

were likely to increase plasma theophylline concentration above the low-dose range of 1-5mg/l. Potential participants were excluded if they fulfilled any of the following criteria.

- Severe or unstable ischaemic heart disease
- A predominant respiratory disease other than COPD
- Any other significant disease/disorder which, in the investigator's opinion, either put the patient at risk because of study participation or might influence the results of the study or the patient's ability to participate in the study
- Previous allocation of a randomisation code in the study or current participation in another interventional study (CTIMP or non-CTIMP)
- For women, current pregnancy or breast-feeding, or planned pregnancy during the study
- Current medication included theophylline
- Known or suspected intolerance to theophylline
- Current use of drugs known to interact with theophylline and/or increase plasma theophylline;[54]

  antimicrobials: aciclovir, clarithromycin, ciprofloxacin, erythromycin, fluconazole, ketoconazole, levofloxacin, norfloxacin;
  cardiovascular: diltiazem, mexiletine, pentoxifylline, verapamil;
  neurological: bupropion, disulfiram, fluvoxamine, lithium;
  hormonal: medroxyprogesterone, oestrogens;
  immunological: methotrexate, peginterferon alpha, tacrolimus;
  miscellaneous: cimetidine, deferasirox, febuxostat, roflumilast, thiabendazole.

Patients with COPD as a consequence of alpha-1-antitrypsin deficiency were excluded however, short or long term use of azithromycin,[56] or use of topical oestrogens or aciclovir were not exclusion criteria.

Identification

Potential participants were recruited from both primary and secondary care sites across the UK. To ensure generalisability the intention was that the majority of participants (>50%) would be recruited from primary care. Recruitment strategies differed between centres depending on local geographic and NHS organisational factors.

Primary care and other community based services

In England recruitment from General Practices was conducted in conjunction with the NIHR Clinical Research Network (CRN) at both the national and local level. Practices could participate as independent research sites or as participant identification centres (PICs) for secondary care or other primary care research sites.

In General Practices the local CRN/collaborating recruitment site/Trial Office liaised directly with practice staff who performed database searches (based on search criteria including use of inhaled preparations containing corticosteroids and record of one exacerbation treated with oral corticosteroids in previous year, interacting medications) to identify potential participants. Potentially suitable patients were sent an invitation letter and a patient information leaflet (PIL). For General Practices acting as independent research sites, interested potential participants were invited to contact the practice-based trial team for more information and to arrange a recruitment visit. For General Practices acting as PICs, interested potential participants were invited to contact the local trial team at the associated secondary or primary care research site for more information and to arrange a recruitment visit. All invitation material, consent forms, trial case report forms and participant completed questionnaires are included in *Supplementary Material 1 – TWICS paperwork.*

In Scotland, the Scottish Primary Care Research Network mirrored the role undertaken by the English CRN by identifying potential participants in primary care, with interested potential participants being invited to make contact with a local trial team based in secondary care.

Potential participants were also identified from other community COPD services such as Pulmonary Rehabilitation, COPD Community Matrons, smoking cessation services and Integrated/Intermediate Care services for patients with COPD. Potentially suitable participants identified by these services were sent an invitation letter and a PIL, and if interested, participants were asked to contact the local trial team (usually in secondary care) for more information and to arrange a recruitment visit.

Secondary care

Potential participants were also identified from patients attending (or who had previously attended) Respiratory Out-Patient appointments or who had been in-patients at the hospitals of the individual recruiting centres. Potentially suitable patients were sent an invitation letter

and a PIL from a member of their hospital care team (usually their consultant). Interested potential participants were invited to contact the local hospital based trial team for more information and to arrange a recruitment visit.

Recruitment/baseline visit

At the recruitment visit, the participant's eligibility was confirmed by a medically qualified doctor and fully informed consent was recorded in writing. Baseline data (see later) were also collected.

Randomisation/treatment allocation

Participants were randomised, usually by a research nurse, using a computerised randomisation system available as both an Interactive Voice Response telephone system and as an internet based application, in reality the internet application was used for all randomisations within the study. The randomisation service was created and administered by the Centre for Healthcare Randomised Trials (CHaRT), University of Aberdeen. Consenting participants were stratified by trial centre (for participants recruited in secondary care) or area (for participants recruited in primary care), and where the participant had been identified (primary or secondary care) and then randomised with equal probability to the intervention (low-dose theophylline) and control (placebo) arms.

The random allocation sequence for TWICS was generated using permuted blocks. This provided randomly generated blocks of entries of varying sizes permuted for each combination of trial centre/area and where the participant had been identified (primary or secondary care). Each entry was assigned a treatment according to a randomly generated sequence utilising block sizes of two or four. Each treatment option was assigned an equal number of times within each block, ensuring that the total entries assigned to each treatment remained balanced. The sequence of blocks was also random, so it was not possible for anyone to determine the next treatment to be allocated based on previous allocations made during the randomisation process.

It was only possible to randomise a participant if the relevant eligibility criteria had been met. In addition to trial centre/area, and where the participant had been identified (primary or secondary care), gender, height, weight, smoking status (and for smokers, number of cigarettes per day) and date of birth was captured during the randomisation process in order

to calculate the correct dosage of study medication for that participant and assign an appropriate drug pack

With this information captured, the randomisation process would assign a Study Number (participant ID), allocate a treatment, and assign a Drug Pack. The user/caller would be notified of the Study Number and Drug Pack either on screen or during the randomisation telephone call. The allocated treatment remained blinded throughout with neither the user/caller nor the participant (or anyone involved in the participant's care or the assessment of outcomes) made aware of the allocation. All the data captured or assigned was saved to a secure database.

The random permuted blocks that defined how treatments were allocated to participants was created by the CHaRT Programming team during the system development process. The system built to utilise these permuted blocks was tested by a run of simulated randomisations which allowed the outcomes to be cross-checked and validated. Before the randomisation system went 'live', enough blocks were created to ensure entries existed for the maximum expected number of participants across the maximum expected number of trial centres/areas. However, the randomisation system was flexible enough to allow the option to add further permuted blocks to the list if more were required during the lifetime of the trial. In such circumstances, randomly generated sequences in blocks of two and four continued to be utilised.

Intervention

The active intervention was Uniphyllin MR 200 mg tablets taken once or twice a day for 52 weeks. The placebo was manufactured to be visually identical, and was taken once or twice a day for 52 weeks. The packaging and labelling of active and placebo interventions were identical. The intervention was for 52 weeks of therapy. The Uniphyllin MR 200mg tablets and placebo were supplied by Napp Pharmaceuticals Limited, Cambridge Science Park, Cambridgeshire, CB4 0GW. Napp Pharmaceuticals Limited is the holder of the marketing authorisation for Uniphyllin MR 200mg tablets (Marketing Authorisation number: PL 16950/0066-0068). Uniphyllin continus 200mg, 300mg and 400mg are licensed for the treatment and prophylaxis of bronchospasm associated with COPD, asthma, and chronic bronchitis, consequently the trial administered theophylline within licensed indication.[54]

Placebo tablets were manufactured by Mundipharma Research Limited, Cambridge Science Park, Milton Road, Cambridge, CB4 0AB.

Dosage

The preclinical studies outlined in chapter 1 demonstrate the critical importance of plasma theophylline concentration, with plasma concentrations 1-5 mg/l having the maximal effect on reducing corticosteroid insensitivity whereas at concentrations >10mg/l theophylline is inhibitory, augmenting corticosteroid insensitivity. Theophylline dosing in TWICS was based upon pharmacokinetic modelling[57-66] of theophylline incorporating the major determinants of theophylline steady state concentration, i.e. weight, smoking status, clearance of theophylline (low, normal, high), and was designed to achieve a steady state (Css) plasma theophylline of 1-5 mg/l and to certainly be <10mg/l, (>10mg is the concentration associated with high dose theophylline, possible side effects and augmentation of corticosteroid insensitivity). Full details are appended in *Appendix 1*.

The dosing of both the interventional arm (Uniphyllin MR 200mg tablets) and control arm (placebo tablets) was determined by the participant's ideal body weight (IBW) and self-reported smoking status.

- A dose of theophylline MR 200 mg (one tablet) once daily (or one placebo once daily) was taken by participants who did not smoke, or participants who smoked but had IBW ≤ 60kg.
- A dose of theophylline MR 200 mg (one tablet) twice daily (or one placebo twice daily) was taken by participants who smoked with IBW > 60 kg.

Ideal body weight was used unless the participant's actual weight was lower than the ideal body weight; in such cases, actual body weight was used to determine dose.

Ideal body weight (IBW) was calculated using the following standard equations.[67]

IBWfemale =45 + 0.9(height in cms-152) kg

IBWmale = 50 + 0.9(height in cms-152) kg

For the calculation of dose, to be classed as a "non-smoker" at recruitment a participant must have abstained from smoking for ≥ 12 weeks. Participants who had given up smoking

recently (less than 12 weeks ago) were classed as a smoker.

Protocol defined changes in dose during treatment period

Table 1 summarises changes in dose during the treatment period based on changes in smoking status or weight.

Table 1: Protocol defined changes in dose during the trial

Characteristics at baseline			**Initial dose**	**Changes to smoking during follow-up**		**Changes to weight during follow-up**	
IBW	***ABW***	***Smoking status***		***Change to smoking***	***Dose change***	***Change to weight***	***Dose change***
>60kg	>60kg	Smoker	bd	Stop Smoking	Reduce to od	Lose ABW<60kg	Reduce to od
>60kg	<60kg	Smoker	od	Stop Smoking	No change	Gain ABW>60kg	Increase to bd
<60kg	>60kg	Smoker	od	Stop Smoking	No change	Lose ABW<60kg	No change
						Gain	No change
<60kg	<60kg	Smoker	od	Stop Smoking	No change	Gain	No change
>60kg	>60kg	Non smoker	od	Start smoking	Increase to bd	Lose ABW<60kg	No change
						Gain	No change
>60kg	<60kg	Non smoker	od	Start smoking	No change	Gain	No change
<60kg	>60kg	Non smoker	od	Start smoking	No change	Lose ABW<60kg	No change
						Gain	No change
<60kg	<60kg	Non smoker	od	Start smoking	No change	Gain	No change

ABW Actual Body Weight, bd twice daily, IBW Ideal Body Weight, kg kilograms, od once daily

Changes in smoking status

Changes in smoking status are known to influence the pharmacokinetics of theophylline (smokers clear the drug more rapidly). Self-reported smoking status was checked at every contact and participants provided with written and verbal advice to contact their study team if

their smoking status changed during the treatment period. Participants who stopped smoking during the treatment period were re-classified as a "non-smoker" if they abstained from smoking for ≥12 weeks. Smoking participants whose IBW (and actual body weight) was >60kg who stopped smoking had their dose reduced to 200mg od (one tablet once a day) [those with IBW<60kg maintained their 200mg od, one tablet once a day dose]. Participants who started smoking during the treatment period were re-classified as a "smoker" when they had smoked for ≥12 weeks. Non-smoking participants whose IBW (and actual body weight) was >60kg who started smoking had their dose increased to 200mg bd (one tablet twice a day).

Changes in weight

Changes in weight are known to influence the pharmacokinetics of theophylline. Smoking participants with an IBW>60kg whose actual body weight fell below 60kg had their dose reduced to 200mg od (one tablet once a day). Smoking participants with IBW>60kg whose actual body weight increased to above 60kg had their dose increased to 200mg bd (one tablet twice a day).

Changes in concomitant medication

When informed of their patient's participation in the trial, General Practitioners were advised to manage their patient for exacerbations as per normal clinical practice but to assume the participant was taking low-dose theophylline. GPs were advised to avoid wherever possible prescribing drugs that were likely to increase plasma theophylline concentrations; they were provided with a list of such drugs. In the event that drugs known to increase theophylline concentration had to be prescribed for 3 weeks or less, GPs/participants were asked to suspend taking the study medication and recommence their study medication after the course of interacting drug had been completed, e.g. prescription of clarithromycin for an exacerbation of COPD. If the interacting drug was to be prescribed for more than 3 weeks, GPs/participants were asked to discontinue the study medication but remain in the study and followed up in accordance with the trial protocol.

Participants were asked to carry a study card and to show this to anyone prescribing medication for them. This advised the prescriber to assume that the participant was taking low-dose theophylline and included a link to the list of drugs that may increase plasma theophylline concentrations.

Theophylline in the form of intravenous aminophylline is sometimes used in the treatment of severe acute exacerbations of COPD in the hospital setting. It was anticipated that during the trial some participants would be hospitalised with life threatening exacerbations of COPD and that the treating physician may wish to use intravenous aminophylline. The commonly used clinical protocol for intravenous aminophylline was established during the era of high-dose oral theophylline when patients would be prescribed oral theophylline aiming for plasma concentration of 10-20mgl and a loading dose of aminophylline would raise plasma theophylline concentrations to toxic concentrations (>20mg/l). For a patient not established on oral theophylline the intravenous protocol comprises a bolus of intravenous aminophylline (usually 250mg, or 5mg/kg) followed by a maintenance dose (0.5mg/kg/hr), whereas for a patient established on oral theophylline the bolus dose is omitted (because of concerns regarding toxicity) and a maintenance infusion (0.5mg/kg/hr) commenced. In the era of high-dose theophylline it was critical to establish if a patient was taking oral theophylline before a physician commenced a patient on intravenous aminophylline.

Pharmacokinetic modelling (*Appendix 1*) of the low-dose theophylline dosing regimen demonstrated that a 250mg (or 5mg/kg if <50kg) loading dose of aminophylline could be administered to trial participants and their plasma theophylline would remain within the therapeutic high-dose bronchodilating concentration of 10-20mg/l (*Appendix 1*). As per Guideline recommendations for plasma theophylline monitoring we advised the measurement of plasma theophylline 24 hours after commencing intravenous aminophylline (allocation status would not be discernible from such a concentration).[24] Study drug was discontinued during intravenous aminophylline therapy, but restarted after discontinuation of intravenous aminophylline therapy.

The advice regarding use of intravenous aminophylline was summarised on the participant's study card. In reality no treating physicians contacted the study team with concerns about intravenous aminophylline.

Supply of study medication

Each participant received their first bottle of four weeks study medication (or placebo) from a participating Clinical Trials Pharmacy. For secondary care sites this was usually the Clinical Trials Pharmacy based at that secondary care site. For participants recruited in primary care

study sites the first bottle of medication was dispensed from the Clinical Trials Pharmacy in NHS Grampian and couriered to the participant's address.

Each participant also received two further supplies of six bottles (each bottle being a four week supply). These supplies were dispatched to participants by a third party (Anderson Brecon, Hereford, UK) and delivered to participants addresses via a courier. These shipments were made around week 3 and week 27 to enable continuity of supply. Receipt of trial medication to the participant's home address was confirmed by signature on receipt.

Data Collection

Baseline, outcome and safety data were collected by face to face assessments conducted at recruitment/baseline (week 0), 6 months (week 26) and 12 months (week 52). Participants were phoned two weeks after starting study medication to ensure that they were tolerating the medication. The schedule for data collection within the study is outlined in *table 2*. If a participant was unable to attend a scheduled follow up assessment visit because of an acute illness e.g. exacerbation of COPD, or other reasons, the visit was postponed and the participant was assessed within four weeks of the scheduled assessment visit. Participants unable to attend for face to face assessment at six and twelve months were followed up by telephone, home visit, or sent the questionnaires to complete at home.

The following data were collected:

Demographic, clinical data

Demographic, contact, clinical history and if necessary clinical examination data were captured at the recruitment visit.

Drug history

Regular use of prescription drugs was recorded at recruitment, and the 6 and 12 month assessments. ICS use was checked at recruitment, 6 and 12 months. Many participants brought they repeat prescription list with them to the assessments. Participants were asked how many times a day they used their ICS preparation and the dose.

Smoking history

Smoking history (age commenced, age ceased, average cigarettes smoked per day) and

current smoking status was recorded at recruitment, and pack year consumption computed. At the six and twelve month assessments current smoking status was recorded.

Table 2: Schedule of study assessments[55]

Assessment	Recruitment	2 weeks (telephone)	Month 6 (face to face)	Month 12 (face to face)	Post study GP records
Assessment of Eligibility Criteria	✓				
Written informed consent	✓				
Demographic data, contact details	✓				
Clinical history	✓				
Drug history	✓		✓	✓	
Smoking status	✓	✓	✓	✓	
Height	✓				
Weight	✓		✓	✓	
Total number COPD exacerbations requiring OCS/antibiotics			✓	✓	✓
Hospital admissions			✓	✓	✓
Health related quality of life	✓		✓	✓	
Disease related health status (CAT, mMRC dyspnoea, HARQ)	✓		✓	✓	
Post bronchodilator lung function	✓		✓	✓	
Adverse events/drug reactions		✓	✓	✓	
Health care utilisation	✓		✓	✓	
Patient Compliance			✓	✓	

OCS oral corticosteroid, CAT COPD Assessment Test, GP General Practice, mMRC modified Medical Research Council dyspnoea scale, HARQ Hull Airways Reflux Questionnaire

Height & weight

Height was measured using clinic stadeometers at baseline. Weight was assessed using clinic scales at recruitment, and the 6 and 12 month assessments.

Number of COPD exacerbations

The primary outcome measure of the total number of COPD exacerbations requiring antibiotics/oral corticosteroids whilst on study medication was ascertained at the 6 and 12 month assessment. Participants were encouraged to record any exacerbations in a space provided on the outer packaging (carton) used to ship medication or on the participant follow-up card, and to bring this to their follow-up assessments. For those participants where follow-

up at 12 months could not be completed, GPs were contacted and asked to provide information on the number of exacerbations experienced by the participant in the treatment period, and whether or not these resulted in hospital admission.

The American Thoracic Society (ATS)/European Respiratory Society (ERS) guideline definition of COPD exacerbation was used: a worsening of patient's dyspnoea, cough or sputum beyond day-to-day variability sufficient to warrant a change in management.[55, 68] The minimum management change was treatment with antibiotics or oral corticosteroids. A minimum of two weeks between consecutive hospitalisations/start of new therapy was necessary to consider events as separate. A modified American Thoracic Society/European Respiratory Society operational classification of exacerbation severity was used for each exacerbation:

Level I, Increased use of their short acting β2 agonist (*mild*);
Level II, use of oral corticosteroids or antibiotics (*moderate*);
Level III, care by services to prevent hospitalisation (*moderate*);
Level IV, admitted to hospital (*severe*).[68]

An exercise to validate patient reported exacerbations was carried out (see *Appendix 2*).

Hospital admissions

The number of unscheduled hospital admissions whilst on study medication was ascertained at the 6 and 12 month assessments. Emergency admissions consequent upon COPD were also identified. Participants were encouraged to record any hospital admissions in the space provided on the outer packaging (carton) used to ship medication or on the participant follow-up card, and to bring this to their follow-up assessments. For those participants where follow-up at 12 months could not be completed, their GP or hospital records were checked to ascertain the number of hospital admissions during the treatment period.

Health related quality of life

Health related quality of life data were captured at recruitment, and at the six and twelve month assessments by questionnaire using the EuroQoL 5D (EQ-5D-3L) Index[69, 70] that has been used widely in studies of COPD. The completed instrument can be translated into quality of life utilities suitable for calculation of quality adjusted life years (QALY)s through the published United Kingdom tariffs.[71]

Disease related health status

Disease related health status was ascertained at recruitment and at the 6 and 12 month assessments by participant completed questionnaire using the COPD Assessment Test (CAT).[72-74] The CAT is an 8-item unidimensional measure of the impact of COPD on patients' health. The CAT has a scoring interval of 0-40, with 0-5 being the norm for healthy non-smokers and > 30 being indicative of very high impact of COPD on quality of life[72]. The CAT is reliable and responsive, correlates very closely with the St George Respiratory Questionnaire and is preferred because it provides a more comprehensive assessment of the symptomatic impact of COPD and is shorter and thus more easy to complete,[72-74]

Participants were also asked to grade their breathlessness using the mMRC dyspnoea scale at recruitment, and the six and twelve month assessments.[75] The mMRC dyspnoea scale has been in use for many years to grade the effect of breathlessness on daily activities. The mMRC dyspnoea scale is a single question which assesses breathlessness related to activities, the scoring interval is 0-4 with 0 being 'Not troubled by breathlessness except on strenuous exercise' and 4 being 'Too breathless to leave the house, or breathless when dressing or undressing'. The mMRC score has been validated against walking test performance and other metrics of COPD health status eg St George Respiratory Questionnaire.[76]

In self-selected recruitment centres, the Hull Airway Reflux Questionnaire (HARQ) was completed by participants at recruitment, 6 and 12 months. The HARQ was used to assess symptoms not elucidated by the CAT or mMRC dyspnoea scale. HARQ is a validated self-administered questionnaire which is responsive to treatment effects.[77]

Post bronchodilator lung function

Lung function was measured at recruitment, and 6 and 12 months using spirometry performed to American Thoracic Society/European Respiratory Society standards.[78] Spirometry is a routine part of the clinical assessment of people with COPD. Post bronchodilator (LABA within 8 hours, short acting β_2 agonist within 2 hours) FEV_1 and FVC were measured. If necessary lung function was measured 15 minutes after administration of the participant's own short acting β2 agonist (SABA). The European Coal and Steel Community (ECSC) predictive equations were used to compute predicted values for FEV_1 and FVC.[79] Where spirometry was contraindicated, or participants were not able to complete spirometry, this was omitted.

Health care utilisation

Health care utilisation during the previous 6 months was ascertained at recruitment and at the 6 and 12 month assessments using a modified version of the Client Service Receipt Inventory (CSRI).[80] The CSRI is a research questionnaire for retrospectively collecting cost related information about participant's use of health and social care services.

Adverse reactions and serious adverse events

This trial complied with the United Kingdom National Health Service Health Research Authority guidelines for reporting adverse events.[81] Adverse reactions (AR) and serious adverse events (SAE) occurring during the 12 month follow-up period were ascertained at the two week telephone call and at the six and twelve month assessments. Participants were notified of recognised adverse reactions and encouraged to contact the local study centre if they experienced these.

Hospitalisations for treatment planned prior to randomisation and hospitalisations for elective treatment of pre-existing conditions were not considered or recorded or reported as an SAE. Complications occurring during such hospitalisation were also not considered, recorded or reported as an SAE – unless there was a possibility that the complication arose because of the study medication (ie a possible adverse reaction). Exacerbations of COPD, pneumonia or hospital admissions as a consequence of exacerbations of COPD or pneumonia were not considered, recorded or reported as AEs or SAEs because they were primary and secondary outcomes for the trial.

Serious adverse events were assessed as to whether the SAE was likely to be related to the treatment using the following definitions:

- Unrelated: where an event is not considered to be related to the study drug
- Possibly: although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
- Probably: the temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug
- Definitely: The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that study drug is the most likely cause

The reference safety information used to assess whether or not the event was expected was section 4.8 of the Summary of Product Characteristics (SmPC) for theophylline.[54]

Compliance

Compliance/adherence and persistence with study medication was assessed at the six and twelve month assessments. Participants were asked to return empty drug bottles and unused medication; compliance was calculated by pill counting.[82] Participants were deemed to be compliant if they had taken 70% or more of the expected doses.

Participant withdrawal

Participants who withdrew from treatment (for example because of unacceptable side effects, or because they were prescribed a contraindicated medicine for longer than 3 weeks) who agreed to remain in the study for follow-up were followed up at 6 and 12 months. Those who did not want to attend for clinical follow-up at 6 and 12 months could be followed up by telephone or home visit, or opt to receive questionnaires at home. Participants who wished to withdraw from study follow-up could continue to contribute follow-up data by agreeing to have data extracted from their primary care and secondary care medical records.

Sample Size

The sample size of 1424 was estimated on the basis of the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study reporting the frequency of COPD exacerbations in 2138 patients.[21] For patients identical to our target population (who in a 1-year period have at least two self-reported COPD exacerbations requiring antibiotics or oral corticosteroids), the mean (standard deviation) number of COPD exacerbations within 1 year was 2.22 (1.86).[21] Given a similar rate in the placebo arm, 669 subjects were needed in each arm of the trial to detect a clinically important reduction in COPD exacerbations of 15% (i.e., from a mean of 2.22 to 1.89) with 90% power at the two-sided 5 % significance level. Allowing for 6% loss to follow-up[83] this was inflated to 712 participants in each study arm, giving 1424 in total.

The sample size of 1424 included 6% loss to follow up based upon a Cochrane Review of oral theophylline in COPD.[83] During the present study, a higher proportion of participants than expected ceased their study medication (although most were not lost to follow-up). With

the appropriate REC and Regulatory Approvals, recruitment continued beyond 1424 in the time available with the total number recruited being 1578 to counteract this loss of person-years on medication. Recruitment ended in August 2016.

Statistical analysis

All analyses were pre-specified in the statistical analysis plan which was approved by both the Trial Steering Committee (TSC) and the Data Monitoring Committee (DMC) in advance of analysis. The statistical analysis plan is included in *Supplementary Material 2 – Statistical Analysis Plan.* Unless pre-specified, a 5% two-sided significance level was used to denote statistical significance throughout and estimates are presented alongside their 95% confidence intervals (CI). No adjustments were made for multiple testing. All analyses were according to the intention to treat principle with a per-protocol analysis performed as a sensitivity analysis. The per-protocol analysis excluded participants who were not compliant, with compliance being defined as taking 70% or more of their expected doses of study medication. All analyses were undertaken in STATA version 14.[84]

Categorical variables are described with number and percentage in each category. Continuous variables are described with mean and standard deviation (SD) if normally distributed and median and inter-quartile range if skewed. The amount of missing data is reported for each variable.

Primary outcome

The primary outcome (number of COPD exacerbations requiring antibiotics and/or oral corticosteroids in the 12 month treatment period following randomisation) was compared between randomised groups using a generalised linear model with log-link function, over dispersion parameter and length of time in study as an offset. The estimated treatment effect is presented as unadjusted rate ratio followed by adjusted rate ratio for a set of pre-specified baseline variables. The adjustment variables were centre (as a random effect), where the participant was identified (primary or secondary care), age (in years) centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, treatment with LAMA/LABA or a combination and treatment with long term antibiotics. Participants that did not provide a full twelve months of follow-up information were included to the point at which they were lost to follow-up with their time in study utilised in the offset variable.

Secondary outcomes

The total number of COPD exacerbations requiring hospital admission and the total number of emergency admissions (all causes) were analysed in the same way as the primary outcome. Occurrence of pneumonia during following up was analysed with mixed effects logit model. Quality of life measures (CAT, EQ-5D-3L, HARQ) and lung function (FEV_1 and FVC) measured at baseline, 6 month follow-up and 12 month follow-up were compared between groups using a mixed effects model unadjusted and adjusted for the same pre-specified covariate set as described for the primary outcome. Fixed effects included visit number, treatment with participant and participant-visit interaction fitted as random effects. A treatment-visit interaction was included to assess the differential treatment effect on rate of change in outcome. An autoregressive (AR(1)) correlation structure was used throughout. All participants within the ITT population were included in the analysis and missing outcome data assumed to be missing at random. Breathlessness as measured by the mMRC dyspnoea scale was analysed using a mixed effects generalized linear model using a logit link function. All-cause mortality rate and COPD related mortality and time to first exacerbation were compared between randomised groups using Kaplan-Meier survival curves and Cox regression for adjustment. Total dose of inhaled corticosteroid at end of follow-up and change in total daily dose from baseline were calculated and compared between randomised groups using an independent samples t-test and linear regression for adjustment. The proportion of participants changing medication during the follow-up period was compared using a chi-squared test.

Sensitivity analyses

To assess the impact of death on the treatment effect for the primary outcome, the total number of exacerbations and the number of exacerbations requiring hospital admission we undertook a sensitivity analysis excluding those participants that died during the study period. A sensitivity analyses for QoL and lung function was also undertaken by repeating the mixed effects models on only those participants who survived the 12 month follow-up only.

Pre-specified sub group analysis

The analysis for the primary outcome was repeated for a number of subgroups. The subgroups were age (< 60, 60 to 69, ≥70 years), gender (male/female), body mass index (<18.5, ≥18.5 to < 25, ≥25 kg/m^2), smoking status at recruitment (ex/current), baseline treatment for COPD (triple therapy (ICS, LAMA, LABA), double therapy (ICS/LAMA or

ICS/LABA), single therapy (ICS only), GOLD stage (I-II, III, IV), exacerbations in 12 months prior to recruitment (2, 3-4, 5+), oral corticosteroids at recruitment (yes/no), dose of inhaled oral corticosteroid at recruitment (1600, ≥1600 µg/day beclomethasone equivalents). Sub group analysis was undertaken by the addition of a treatment*covariate interaction term and using the 'lincom' command in STATA to obtain group specific estimates. We report observed mean (SD) exacerbations in each subgroup by treatment group, the treatment effect (IRR and 99% CIs) along with the p-value for the interaction term. Due to the exploratory nature of the subgroup analysis we used 99% CIs.

Health Economics

Resource Use

Health care utilisation during the previous 6 months was collected at the 6 and 12 month assessments using a modified version of the Client Service Receipt Inventory (CSRI).[85] The CSRI is a research questionnaire for retrospectively collecting cost related information about participant's use of health and social care services. The main resource uses collected during the follow-up period were:

- Theophylline intervention
- Costs of exacerbation treatment, this was broken down into two groups of costs: the location of the treatment; 'home', 'care by services to prevent hospitalisation' and 'admitted to hospital'; and the treatment cost of the exacerbations, including medication
- Cost of COPD maintenance medications
- Other health service use (including inpatient, out-patient and primary care use), none of these included exacerbation costs.
- Non-COPD emergency hospital admissions
- Regular medication

Baseline resource use was collected for current use of COPD maintenance treatment and regular medication. For calculating baseline resource use and costs we have assumed this usage to be for the six months prior to baseline. The number of exacerbations needing treatment in the previous 12 months and the number of exacerbations resulting in hospitalisation in the previous 12 months were also collected.

Unit costs

All resource use was valued in GBP (£ sterling) and indexed to 2016, using the Health Service Cost Index[86] to adjust if necessary.

- Medication costs were obtained from the British National Formulary (BNF).[87]
- For exacerbations, non-COPD emergency admissions, inpatient stays, outpatient attendances, and primary care, costs were obtained from; NHS reference costs,[88] Information Services Division (ISD),[89] Personal Social Services Research Unit (PSSRU),[86] BNF[87] and papers by Oostenbrink et al[90] and Scott et al.[91]

The total cost per participant was calculated by assigning unit costs to resource use for each participant. Total mean costs were calculated using a generalised linear model (GLM) model with a gamma family and clustering for centre number. After multiple imputation total costs were adjusted for baseline characteristics using standard regression methods, to account of any differences in cost related variables at baseline.[92]

Unit costs and their sources are presented in *table 3*.

Table 3: Unit costs and sources

Resource	Unit	Unit cost	Source
Intervention			
Theophylline	200mg od	£0.05	BNF[87]
	200mg bd	£0.11	BNF[87]
Exacerbation treatment			
Oxygen	Per day	£19	Oostenbrink[90]
Medication	Daily dose	Various	BNF[87]
Inpatient costs			
Ward stay (elective)	Bed day	£362	NHS reference costs 2015/16 (elective excess bed day unit cost)[88]
Ward stay (non-elective)	Bed day	£298	NHS reference costs 2015/16 (non-elective excess bed day unit cost)[88]
COPD related ward stay	Bed day	£262	NHS reference costs 2015/16 (weighted average of COPD hospital stays DZ65)[88]
Long stay ward	Day	£133	PSSRU 2016 (Not for profit care home fee, mean £931 per week)[86]

Table 3 (continued): Unit costs and sources

Resource	Unit	Unit cost	Source
Outpatient costs			
Day case	Day	£521	ISD costs book 2015/16 (Day cases all specialities)[89]
Outpatient appointment	Appointment	£177	NHS reference costs 2015/16 (Total outpatient attendances unit cost)[88]
Primary care costs			
Emergency GP visit	Per contact	£86	Based on Scott et al for Out of Hours home visit[91]
Routine GP visit	Per contact	£31	PSSRU 16 (inc direct care staff costs, without qualifications - 9.22 minutes)[86]
Community/district nurse	Per contact	£38	NHS ref costs 2015/16 (Community Health Services - N02AF - District nurse)[88]
Hospital at home team	Per contact	£84	NHS ref costs 2015/16 (Community Health Services - N08AF - Specialist nursing Asthma and respiratory nursing liaison)[88]
GP telephone	Per contact	£23.43	PSSRU 2016 (including direct care staff costs, without qualification costs 7.1 minutes)[86]
GP home visit	Per contact	£77.22	PSSRU 2016 (including direct care staff costs, without qualification costs 11.4 minutes visit plus 12 minutes travelling time)[86]
Blood test	Per contact	£14.42	ISD costs book 2016 (laboratory services, haematology plus practice nurse appointment, PSSRU 2016)[86]
Dental service	Per contact	£77	NHS reference costs 2015/16 (general dental service attendance)[88]
Hearing aid clinic	Per contact	£53	NHS reference costs 2015/16 (audiology)[88]
Occupational therapist	Per contact	£79	NHS reference costs 2015/16 (occupational therapist)[88]

Table 3 (continued): Unit costs and sources

Resource	Unit	Unit cost	Source
Diabetic nurse	Per contact	£71	NHS reference costs 2015/16 (specialist nursing, diabetic)[88]
Cardiac nurse	Per contact	£81	NHS reference costs 2015/16 (specialist nursing, cardiac)[88]
Long term condition nurse/community matron	Per contact	£89	NHS reference costs 2015/16 (Active case management)[88]
Paramedic	Per contact	£181	NHS reference costs 2015/16 (ambulance, see, treat, refer)[88]
Chiropodist/community clinic/endoscopy	Per contact	£60	NHS reference costs 2015/16 (mean of community health services, no separate chiropodist or community clinic cost)[88]
Physiotherapist	Per contact	£49	NHS reference costs 2015/16 (physiotherapist)[88]
Podiatrist	Per contact	£40	NHS reference costs 2015/16 (podiatrist)[88]
Practice nurse	Per contact	£9.42	PSSRU 2016 (nurse GP practice, 15.5 minutes per contact)[86]
Speech therapist	Per contact	£88	NHS reference costs 2015/16 (speech and language therapist)[88]
Nurse telephone call	Per contact	£6.10	PSSRU 2016 (nurse led triage)[86]
Treatment room nurse	Per contact	£27	NHS reference costs 2015/16 (specialist nursing, treatment room)[88]
Urine sample/sputum test	Per contact	£10.28	ISD costs book 2016 (clinical chemistry, plus practice nurse appointment, PSSRU 2016)[86]
Dietician	Per contact	£81	NHS reference costs 2015/16 (dietician)[88]
Flu jab	Per contact	£14.67	BNF plus practice nurse appointment, PSSRU 2016[86]
Early support discharge	Per contact	£124	NHS reference costs 2015/16 (crisis response and early discharge services)[88]
Diagnostic imaging	Per contact	£37.3	NHS reference costs 2015/16 (total outpatient attendances, diagnostic imaging)[88]

Table 3 (continued): Unit costs and sources

Resource	Unit	Unit cost	Source
Optometry	Per contact	£79.19	NHS reference costs 2015/16 (total outpatient attendances, optometry)[88]
Healthcare assistant	Per contact	£6.20	PSSRU 2016 (band 3 nurse, 15.5 minutes)[86]
Talking matters	Per contact	£24.06	PSSRU 2009/10 (counselling services in primary care, telephone consultation 29.7 minutes)[86]
Community psychiatric nurse/stroke nurse	Per contact	£77	NHS reference costs 2015/16 (other specialist nursing)[88]
Counselling	Per contact	£78.27	PSSRU 2009/10 (counselling services in primary care, consultation 96.6 minutes)[86]
Breast care nurse	Per contact	£59	NHS reference costs 2015/16 (beast care nursing)[88]
Community mental health team	Per contact	£121	NHS reference costs 2015/16 (other mental health specialist team)[88]
Pulmonary rehabilitation	Per contact	£78	NHS reference costs 2015/16 (other single condition community rehabilitation teams)[88]
Emergency costs			
Ambulance	Per attendance	£236	NHS reference costs 2015/16 (See, treat convey)[88]
Accident and Emergency attendance	Per attendance	£138	NHS reference costs 2015/16 (Emergency medicine average unit cost)[88]

bd twice daily, BNF British National Formulary, ISD Information Services Division, NHS National Health Service, od once daily, PPSRU Personal Social Services Research Unit

Health Outcomes

The economic outcome used was the quality adjusted life-year (QALY); a combination of quality and quantity of life. The quality of life measure was generated using completed EQ-5D-3L questionnaires. Participants completed the questionnaire at baseline, 6 months and 12 months.

Patient-reported health-related quality of life obtained from EQ-5D-3L questionnaires were valued in terms of utilities (from a scale of -0.59 to 1, where 1 is full health) using a standard UK value set,[71] which were converted into QALYs using standard area-under-the-curve methods; patient utility measurements from each follow-up point were weighted by the time interval between follow-up points. Discrete changes in utility values between follow-up time points were assumed to be linear. After multiple imputation QALYs were adjusted for baseline characteristics using standard regression methods.

Analysis

The total cost per participant in each intervention was summed and divided by the number of participants in each arm to calculate the total mean cost per participant in each arm, along with the difference in means and a 95% confidence interval (CI).

The mean QALY per participant for each intervention was calculated by summing all participant's QALYs and dividing by the number of participants in that intervention arm. The difference in the means were also calculated along with a 95% CI.

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in mean costs by the difference in mean QALYs. The National Institute for Health and Clinical Excellence (NICE) threshold of £20,000 to £30,000 was used when judging whether the intervention was cost-effective.[93]

Withdrawn participants were included in the analysis and the total time they spent in the trial was used to adjust total costs and QALYs using regression methods.

To explore the uncertainty around the cost and QALY differences and the resulting ICER, a non-parametric bootstrapping technique was employed with 1,000 iterations, results are presented using a cost-effectiveness plane, showing all 1,000 incremental cost-effectiveness pairs, and a cost-effectiveness acceptability curve.

The analysis was carried out using STATA 14.0.[84]

Missing data

There was a small amount of multivariate missingness in collected resource data.

Resource use data were not available for some exacerbations, either because this was not reported by participants, or only limited data were available from GP or hospital records. Missing resource use data on exacerbations were dealt with as detailed below:

- For exacerbations with missing length of exacerbation data, the length was assumed to be the mean, treatment arm specific, length of exacerbation.
- For exacerbations missing a marker to indicate the location of treatment this was assumed to be at home, as the majority of location of treatments were at home (over 80%).
- For exacerbations treated in hospital, missing lengths of stay were assumed to be the length of exacerbation.
- For exacerbations missing treatment costs a treatment arm specific mean cost of treatment was assumed.

At a resource use level there were small amounts of missing data which were dealt with as described below:

- Where the length of stay data was missing for emergency hospital admissions, this was imputed using the treatment arm specific mean length of stay.
- Where participants had no observations completed to indicate the duration of a maintenance COPD treatment, it was assumed that the treatment duration was for the 6 months prior to the date that information about the COPD maintenance treatment was collected.
- Where a participant had indicated that they received a maintenance COPD treatment but no medication details were available, a treatment arm specific mean cost was imputed for that specific maintenance medication.
- Where resource use was missing for inpatient, outpatient and primary care service use, the participant was assumed not to have used the resource in question.

Complete cases were analysed initially and multiple imputation was used to explore the effect of missing data on the analysis.

The multiple imputation technique used was multiple imputation using chained links (MICE). Multiple imputation assumes that data is missing at random; missing data may depend on observed data.

Assumptions

The following assumptions were made in the health economics analysis:

- Complete case is defined as having data covering resource use for the 12 month follow-up period. For a small number of participants there was no 6 month data collection, however the 12 month data collection covered resource use for the whole of the 12 month follow-up period.

Public and patient involvement (PPI)

A patient with COPD was an independent voting member of the TSC. Initially this was a patient from the Aberdeen Chest Clinic who was nominated by Chest Heart and Stroke Scotland as part of their Voices Scotland initiative. In 2015 this patient had to resign from the TSC because of ill-health and was replaced by another patient from the Aberdeen Chest Clinic who is a patient living with COPD.

Early versions of the trial protocol and PILs were reviewed by a representative from the British Lung Foundation-North Region, and a patient who lives with COPD and attends the Chest Clinic at the Freeman Hospital, Newcastle. They both attended the Trial Initiation Meeting, purposively held in Newcastle in February 2013 and contributed suggestions and changes to the final study design that were reflected in the protocol and PIL.

The TWICS trial was publicised in 2014 by a press release that included supportive quotes from the British Lung Foundation and Chest Heart and Stroke Scotland, this publicity resulted in members of the public with COPD volunteering to participate, with their permission their details were passed on to their local TWICS study site.

We anticipate that the PPI member of the Trial Steering Committee will comment on results letter to be sent to trial participants. It is also anticipated that the publication of the trial results will be co-ordinated with press releases from the participating academic/NHS institutions, British Lung Foundation and Chest Heart and Stroke Scotland. Members of the study team will be participating in local Public Engagement with Research activities.

Protocol amendments

There were seven protocol amendments and these are summarised in *table 4*.

Table 4: Summary of protocol amendments.

Version number, date	Summary of amendments
Version 2, 20 June 2013	Version initially approved by REC.
Version 3, 5 August 2013	To incorporate clarification of the definition of smoker and non-smoker as required by MHRA.
Version 4, 5 February 2014	To add episodes of pneumonia as a secondary outcome and to confirm that pneumonia will not be classified as an AE or SAE within the trial; To clarify that, in addition to the study intervention, participants will receive "usual NHS care" in the treatment of COPD rather than guideline compliant care; To clarify that patients with Alpha-1-Antitrypsin Deficiency and COPD should be excluded.
Version 5, 2 July 2014	To clarify when spirometry may be contraindicated; To update the version of the SmPC appended to the protocol; To include the definition of the source data
Version 6, 4 August 2014	To list additional potential avenues for identification of eligible patients (including smoking cessation clinics, community spirometry clinics and other services for patients with COPD); To confirm that participants with limited mobility or who live some distance from the study site can be recruited during a home visit.
Version 7, 11 August 2015	To update the telephone number for the switchboard at Aberdeen Royal Infirmary (for emergency unblinding); To describe how cases where medications that potentially interact with theophylline are prescribed to trial participants are documented within the trial.
Version 8, 19 May 2016	To amend the protocol to allow for over-recruitment.
Version 9, 14 April 2017	To describe how requests for unblinding made by participants (or their GPs) at the end of their 12 month follow-up should be handled; To revise the planned validation exercise in relation to participant reported exacerbations.

AE Adverse Event, COPD Chronic Obstructive Pulmonary Disease, GP General Practitioner, MHRA Medicines and Healthcare products Regulatory Agency, NHS National Health Service, REC Research Ethics Committee, SAE Serious Adverse Event, SmPC Summary of Product Characteristics

Trial oversight

A Trial Steering Committee, with independent members, including PPI, oversaw the conduct and progress of the trial. An independent Data Monitoring Committee oversaw the safety of subjects within the trial.

Breaches

Breaches of trial protocol or GCP were recorded and reported to the sponsor. A summary of breaches is included in *Appendix 3*. Participants who were the subject of a breach remain in the intention to treat population, the safety population and the per protocol population (if compliance criteria were met).

CHAPTER 3 – BASELINE CHARACTERISTICS

Recruitment

Participants were recruited to the trial between February 2014 and August 2016. During this 31 month period, 141 UK sites were opened to recruitment. Once opened, some sites (n=20) failed to recruit any patients to the study. Reasons for this included staff changeover, lack of eligible patients, competing priorities, practice closure and eligible patients who did not agree to take part.

In total, 1578 participants were recruited from 121 sites (see *table 5*). A detailed summary of recruitment, by site, is given in *Appendix 4*. In summary, across 33 secondary care sites, 1101 participants were recruited, and across 88 primary care sites, 477 participants were recruited. Of those recruited in secondary care, 464 participants were identified in primary care. Overall, 59.6% of participants were identified in primary care.

Table 5: Summary of recruitment

Recruitment site based in	Participants identified in	Number of participants
Secondary care	*Secondary care*	637
Secondary care	*Primary care*	464
Primary care	*Primary care*	477

The initial funding included a 24 month recruitment period. There were delays in manufacturing and packaging the study medication, and the projected recruitment was re-profiled across 21 months. After around six months of recruitment, it became clear that we were unlikely to meet the recruitment target within 21 months. To address this, several measures were successfully implemented: 'second' and 'third' wave sites were opened up earlier than planned; additional primary and secondary care sites were identified and a rolling programme of opening these sites up was established; a six month extension to recruitment was granted by the funder; and we were able to accommodate additional recruitment time within the existing funding. Within the 31 month recruitment period, we were granted approval to over-recruit beyond the original target of 1424 participants. The justification for this was the higher than anticipated numbers of participants who ceased taking the study medication (see chapter 5, section on treatment adherence/compliance for more information).

Figure 3 shows the original recruitment targets, the re-profiled recruitment targets (to accommodate the delay in manufacturing/packaging), our revised recruitment targets (after the extension to recruitment was granted) and the actual recruitment.

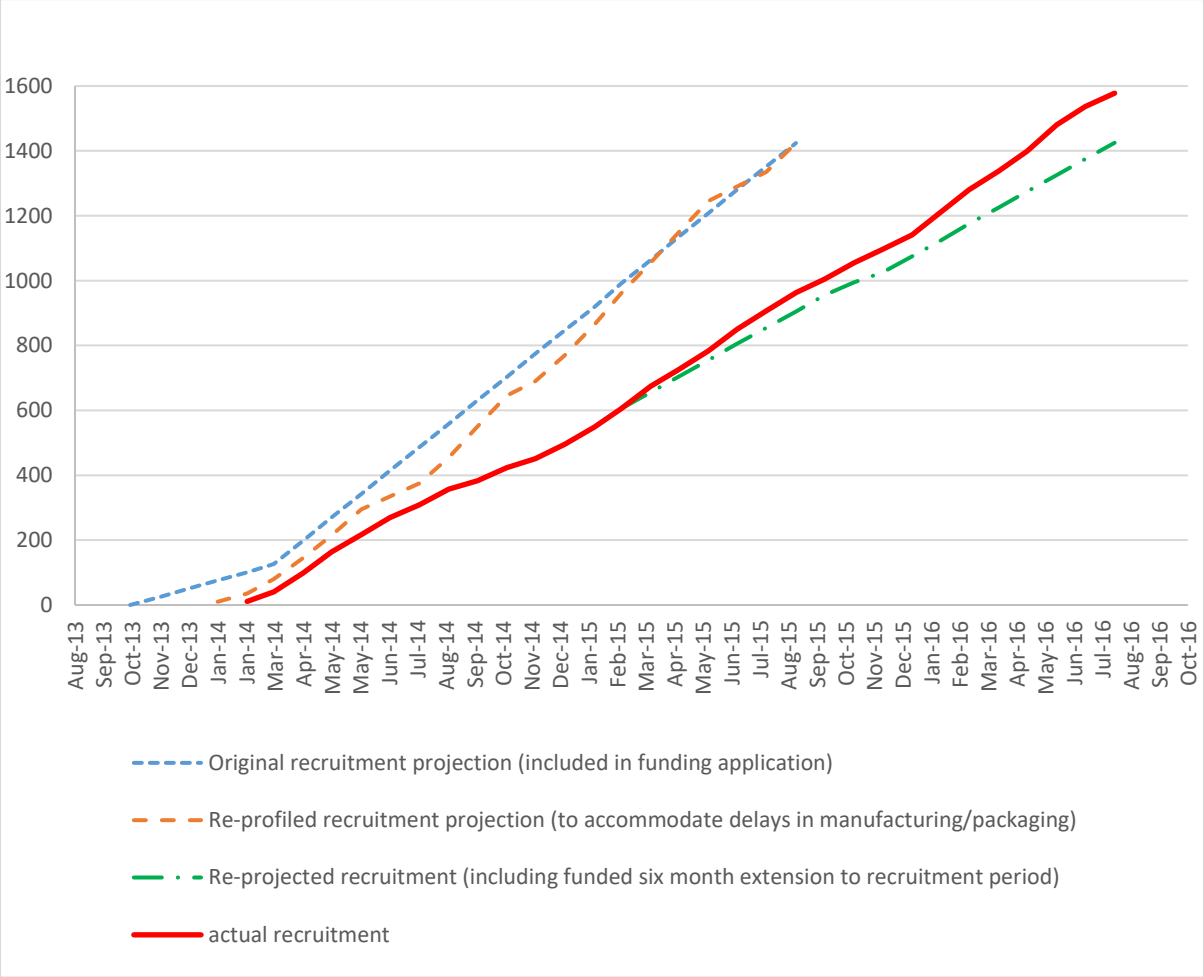


Figure 3: Recruitment

Post randomisation exclusions

Eleven participants were recruited in error and were then excluded. None of these participants took any dose of study medication and are excluded from all study analyses. Reasons for these post-randomisation exclusions are given in *table 6*.

Table 6: Reasons for post-randomisation exclusion

Overarching reason for post-randomisation exclusion	Specific reason for post-randomisation exclusion
Concomitant medications	Already taking a form of theophylline (n=1)
	Concomitant prescription of diltiazem (n=2)
	Concomitant prescription of methotrexate (n=1)
	Not currently prescribed inhaled corticosteroid (n=1)
COPD diagnosis	Diagnosed with right middle lobe collapse not COPD (n=1)
	COPD diagnosis disputed by consultant (n=1)
	Less than two exacerbations in the previous year (n=3)
Spirometry	Did not fulfil spirometric criteria for the study (n=1)

COPD Chronic Obstructive Pulmonary Disease

Sixteen participants who were recruited into TWICS were subsequently noted to be ineligible for the study at the point of recruitment. All sixteen participants had taken at least one dose of study medication and were retained in follow-up and included in the study analyses. Seven of these were taking a form of diltiazem at recruitment, and were identified during a review of all baseline medication recorded for participants. Diltiazem can cause a slight increase in serum theophylline concentration, however any effect is usually clinically insignificant.[94] One of these participants took study medication for approximately 10 days but stopped because they experienced symptoms considered likely to be related to theophylline. A further participant experienced some symptoms that may have been side effects related to the study medication and stopped after approximately four months. One further participant experienced some symptoms that may have been side effects related to study medication but did not cease taking study medication.

In this same review, a further five participants were noted to have been taking a contraindicated medication at baseline. Three participants were noted to be taking a form of oestrogen. Serum theophylline concentration is slightly increased by concomitant oestrogen but no toxicity has been reported.[94] Two participants co-prescribed oestrogen continued to take study medication through their 12 month follow-up with no adverse reactions. The other

participant experienced symptoms (thought to be related to theophylline) and stopped taking the study medication after 14 days. One participant was noted to have been taking febuxostat at recruitment. They had taken study medication through their 12 month follow-up and experienced symptoms that may have been side effects related to study medication. High-dose febuxostat has been reported to possibly increase serum theophylline.[94] One participant was noted to have been taking roflumilast at recruitment. Although roflumilast has no reported effect on serum theophylline concentrations the two drugs act through phosphodiesterase enzymes[94] albeit theophylline at conventional 'high dose' levels with serum concentrations of 10-20mg/l. This participant had taken study medication throughout their 12 month follow-up without any adverse reactions.

Three participants were taking a form of theophylline at recruitment. In two of these, this was only noted after the participant had completed their 12 month follow-up (and the participants had taken study medication through their 12 month follow-up). In the other participant, this was noted after the participant had taken study medication for 8 days and the study medication was then stopped. In all three cases, no adverse reactions relating to the study medication were noted.

One participant was recruited into TWICS when they were already participating in another CTIMP for an unrelated condition. The participant did not disclose this at the time of recruitment and it was not clearly documented in their hospital notes. No interaction between the TWICS study medication and the medication used within the other study is likely. The participant continued to take study medication for approximately eleven months, when a non-related throat problem caused problems in taking the study medication.

Baseline characteristics

Baseline characteristics are presented for the 1567 included participants (after exclusion of the 11 post randomisation exclusions). The theophylline and placebo groups were well balanced in terms of demographic and disease characteristics at baseline.

The mean age of participants was 68.4 years (SD 8.4) (*see table 7*). Just over half of the participants (53.8%) were male. Approximately one third (31.7%) were current smokers; the remainder were ex-smokers. The median pack years smoked was 42 (IQR 27.7, 56.0) pack years. Mean BMI was 27.2 kg/m^2 (SD 6.1).

The median number of participant reported exacerbations in the 12 months prior to recruitment was 3 (IQR 2, 4), the mean number of exacerbations was 3.6 (SD 2.2) (*see table 8*). The majority of participants (79.9%) were prescribed the 'triple therapy' combination of ICS, LABA and LAMA at baseline. Almost one fifth (16.7%) were prescribed ICS and LABA. The remainder were prescribed ICS only (2.0%) or ICS and LAMA (1.5%).

Co morbidities, as reported by participants, were relatively common. Almost one fifth (18.3%) had a concurrent diagnosis of asthma. Four percent of participants reported a diagnosis of bronchiectasis. Just over one third of participants (38.2%) reported a diagnosis of hypertension. Thirteen percent reported ischaemic heart disease and 6.7% reported a previous cerebrovascular event. Almost one third (28.0%) reported anxiety or depression in the last five years. Eleven percent had a diagnosis of diabetes mellitus and 12.8% had a diagnosis of osteoporosis.

Measurement of lung function at baseline revealed that the mean FEV_1 was 51.7 (SD 20.0) percent predicted. Using the GOLD classification,[1] 13.6% were classified as very severe COPD, 37.7% as severe, 39.6% as moderate and 9.2% as mild.

The mean score on the COPD assessment test (CAT) was 22.6 (SD 7.7) indicating that overall, COPD was having a high impact on the lives of participants (*see table 9*). Considering the cut-offs used to interpret scores derived from the CAT, COPD was having a low impact on the lives of 5.3% of participants, in 29.9% COPD was having a medium impact, in 44.4% COPD was having a high impact and in 20.4% COPD was having a very high impact on their lives.

The mean EQ-5D-3L utility score was 0.63 (SD 0.28). The mMRC dyspnoea score revealed that 7.1% of participants were too breathless to leave the house; 27.6% had to stop for breath after walking about 100 metres, 31.5% walked slower than contemporaries on level ground because of breathlessness, 28.3% became short of breath when hurrying or walking up a slight hill, only 5.5% of participants were not troubled by breathlessness except on strenuous exercise.

A comparison of the participants recruited in primary and secondary care indicated that those identified in secondary care were slightly younger, more likely to be ex-smokers, greater number of exacerbations in previous 12 months, higher proportion with more severe COPD, more on triple (ICS/LAMA/LABA) therapy and on long term antibiotic use, there was also a significantly greater prevalence of co-morbidities: bronchiectasis, IHD, osteoporosis *(Appendix 5; Table 34).* Participants recruited in secondary care had a higher CAT score, and slightly lower QoL.

Table 7: Baseline sociodemographic characteristics

	Theophylline			**Placebo**			**Overall**		
Sex									
Male (N, n, %)	788	425	53.9	779	418	53.7	1567	843	53.8
Female (N, n, %)	788	363	46.1	779	361	46.3	1567	724	46.2
Age (N, Mean, SD)	788	68.3	8.2	779	68.5	8.6	1567	68.4	8.4
Smoking status									
Current smoker (N, n, %)	788	247	31.3	779	249	32.0	1567	496	31.7
Ex-smoker (N, n, %)	788	541	68.7	779	530	68.0	1567	1071	68.3
Pack years (N, Mean, SD)	785	47.0	26.3	775	47.1	30.6	1560	47.1	28.5
Pack years (N, Median, IQR)	785	43.0	28.5, 57.0	775	41.0	27.0, 55.0	1560	42.0	27.7, 56.0
BMI (N, Mean, SD)	788	27.1	6.2	779	27.3	6.0	1567	27.2	6.1
BMI group									
Underweight (N, n, %)	788	37	4.7	779	38	4.9	1567	75	4.8
Normal (N, n, %)	788	285	36.2	779	246	31.6	1567	531	33.9
Overweight (N, n, %)	788	252	32.0	779	266	34.1	1567	518	33.1
Obese (N, n, %)	788	214	27.2	779	229	29.4	1567	443	28.3

BMI Body Mass Index, SD Standard Deviation, IQR Interquartile range

Table 8: Baseline clinical characteristics

	Theophylline			**Placebo**			**Overall**		
Exacerbations in the last 12 months (N, mean, SD)	785	3.6	2.2	773	3.5	2.1	1558	3.6	2.2
Exacerbations in the last 12 months (N, median, IQR)	785	3	2, 4	773	3	2, 4	1558	3	2, 4
Exacerbations requiring hospitalisation in the last 12 months (N, mean, SD)	784	0.4	0.8	773	0.4	1.0	1557	0.4	0.9
Exacerbations requiring hospitalisation in the last 12 months (N, median, IQR)	784	0	0, 1	773	0	0, 0	1557	0	0, 0
GOLD 2011 category									
C- ≥2 exacerbations in last year, mMRC 0-1 and CAT<10 (N, n, %)	779	37	4.7	768	45	5.9	1547	82	5.3
D ≥2 exacerbations in last year, mMRC ≥2and CAT≥10 (N, n, %)	779	742	95.3	768	723	94.1	1547	1465	94.7
FEV_1 % predicted (N, mean, SD)	785	51.3	20.1	771	52.2	19.8	1556	51.7	20.0
FEV_1 % predicted category									
80+% [*GOLD mild*] (N, n, %)	785	70	8.9	771	73	9.5	1556	143	9.2
50-79.9% [*GOLD moderate*] (N, n, %)	785	308	39.2	771	308	39.9	1556	616	39.6
30-49.9% [*GOLD severe*] (N, n, %)	785	291	37.1	771	295	38.3	1556	586	37.7
0-29.9% [*GOLD very severe*] (N, n, %)	785	116	14.8	771	95	12.3	1556	211	13.6
FVC % predicted (N, mean, SD)	783	84.3	22.3	770	86.2	23.4	1553	85.2	22.8
FEV_1/FVC ratio (N, mean, SD)	783	49.0	19.7	770	48.5	14.1	1553	48.8	17.1

Table 8 (continued): Baseline clinical characteristics

	Theophylline			**Placebo**			**Overall**		
Current treatment for COPD									
Inhaled Corticosteroid									
ICS only (N, n, %)	788	14	1.8	779	17	2.2	1567	31	2.0
ICS LABA (N, n, %)	788	136	17.3	779	125	16.0	1567	261	16.7
ICS LAMA (N, n, %)	788	13	1.6	779	10	1.3	1567	23	1.5
ICS LABA/LAMA (N, n, %)	788	625	79.3	779	627	80.5	1567	1252	79.9
Oral mucolytic use (N, n, %)	784	201	25.6	771	197	25.6	1555	398	25.6
Long-term antibiotic use (N, n, %)	784	51	6.5	771	48	6.2	1555	99	6.4
Co-morbidities									
Asthma (N, n, %)	782	138	17.6	772	147	19.0	1554	285	18.3
Bronchiectasis (N, n, %)	782	41	5.2	770	27	3.5	1552	68	4.4
Ischaemic Heart Disease (N, n, %)	781	111	14.2	771	96	12.5	1552	207	13.3
Hypertension (N, n, %)	782	317	40.5	772	277	35.9	1554	594	38.2
Diabetes Mellitus (N, n, %)	782	83	10.6	772	93	12.0	1554	176	11.3
Osteoporosis (N, n, %)	783	109	13.9	771	90	11.7	1554	199	12.8
Anxiety/depression treated in last 5 years (N, n, %)	782	222	28.4	772	213	27.6	1554	435	28.0
Cerebrovascular event (N, n, %)	783	46	5.9	772	58	7.5	1555	104	6.7

FEV_1 Forced expiratory volume in 1 second; FVC Forced vital capacity; GOLD Global Initiative for Chronic Obstructive Lung Disease, ICS Inhaled corticosteroid, SD Standard deviation, IQR interquartile range, LABA Long acting β2 agonist; LAMA Long-acting muscarinic antagonists, SD standard deviation

Table 9: Baseline patient reported symptoms and quality of life

	Theophylline			**Placebo**			**Overall**		
Degree of breathlessness (mMRC dyspnoea) [75]									
Not troubled by breathlessness except on strenuous exercise (N, n, %)	783	35	4.5	772	50	6.5	1555	85	5.5
Short of breath when hurrying or walking up a slight hill (N, n, %)	783	216	27.6	772	224	29.0	1555	440	28.3
Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace (N, n, %)	783	251	32.1	772	239	31.0	1555	490	31.5
Stops for breath after walking about 100 metres or after a few minutes on level ground (N, n, %)	783	225	28.7	772	204	26.4	1555	429	27.6
Too breathless to leave the house, or breathless when dressing or undressing (N, n, %)	783	56	7.2	772	55	7.1	1555	111	7.1
COPD assessment test (N, mean, SD)	780	22.8	7.5	771	22.3	7.9	1551	22.6	7.7
COPD assessment test group									
Low (score 0-9) (N, n, %)	780	37	4.7	771	45	5.8	1551	82	5.3
Medium (score 10-19) (N, n, %)	780	219	28.1	771	244	31.6	1551	463	29.9
High (score 20-29) (N, n, %)	780	361	46.3	771	328	42.5	1551	689	44.4
Very high (score 30-40) (N, n, %)	780	163	20.9	771	154	20.0	1551	317	20.4
EQ-5D-3L utility (N, mean, SD)	785	0.62	0.28	772	0.63	0.28	1557	0.63	0.28
EQ-5D-3L VAS (N, mean, SD)	785	59.6	19.0	770	60.8	19.1	1555	60.2	19.1

COPD Chronic Obstructive Pulmonary Disease, EQ-5D-3L EuroQoL 5 dimension 3 level, mMRC modified Medical Research Council, SD standard deviation, VAS visual analogue scale, SD Standard deviation

CHAPTER 4 – CLINICAL EFFECTIVENESS

Clinical effectiveness of low-dose theophylline compared to placebo

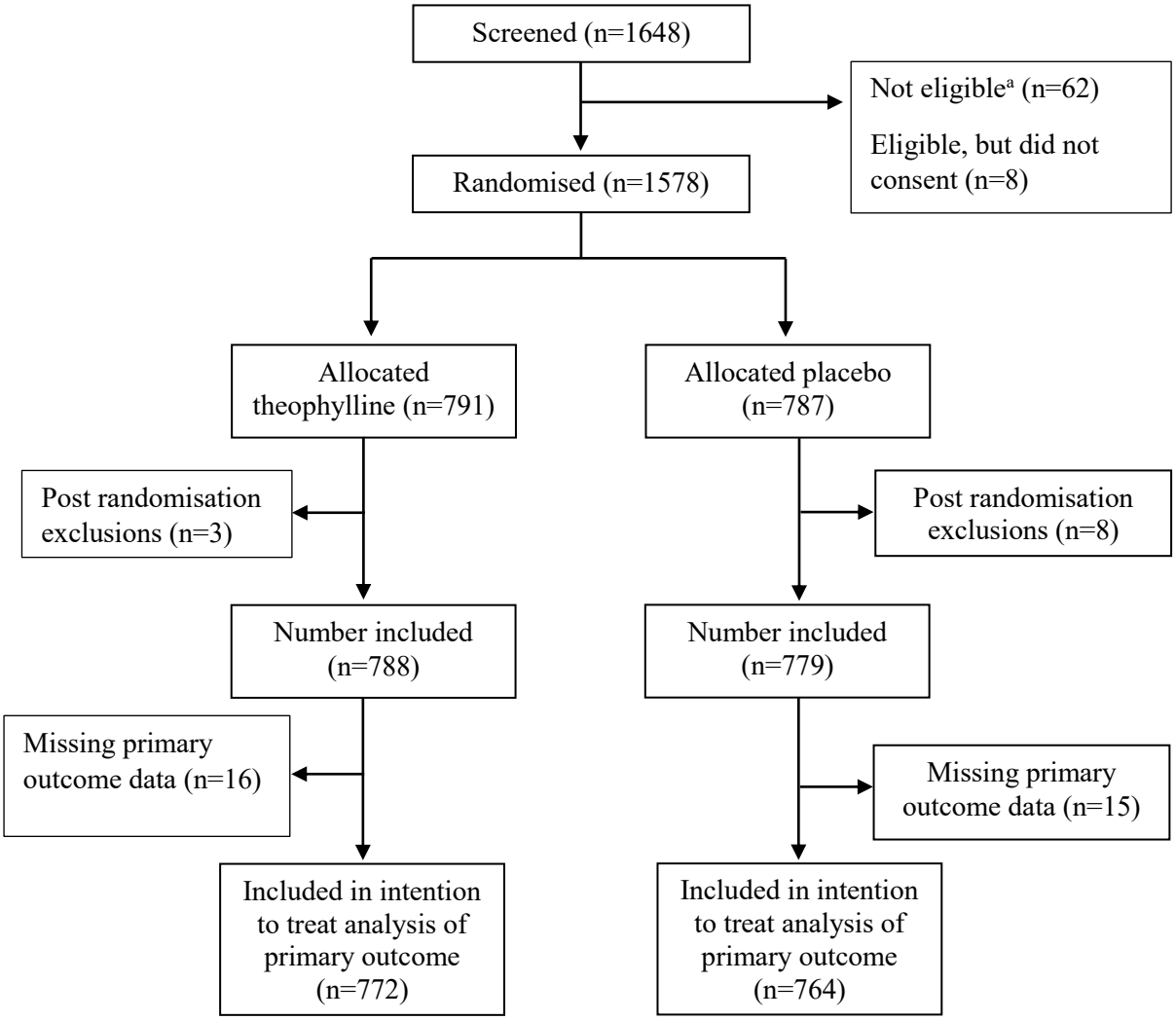
In this chapter we report the results of people with COPD being treated for one year with low-dose theophylline compared with placebo. There were 1578 participants randomised to theophylline or placebo, with 11 post-randomisation exclusions resulting in 1567 participants eligible to initiate study medication and for whom baseline characteristics have been reported (Chapter 3). Follow-up data were unavailable for 31 (2%) participants (16 theophylline, 15 placebo), and the results presented for the intention to treat analysis are based on 1536 participants (772 theophylline, 764 placebo), see *figure 4*. In total there were 1489 person years of follow-up data, with 747 person years in the theophylline group and 742 person years in placebo (*see table 10*).

Intention to treat (ITT) analysis

Primary outcome: total number of exacerbations of COPD requiring a change in management

In total 633/772 (82.0%) of participants allocated to theophylline had at least one exacerbation, with 1727 exacerbations in the group overall. For participants allocated to placebo 609/764 (79.7%) had at least one exacerbation and there were 1703 exacerbations in the group overall. The mean (SD) number of exacerbations per participant was 2.24 (1.99) in those allocated to low-dose theophylline and 2.23 (1.97) in those allocated to placebo. The adjusted incidence rate ratio (IRR) and 95% CI for exacerbation was 0.99 (0.91, 1.08), indicating no difference in the exacerbation rate during the 12 month follow-up period for those on low-dose theophylline compared with placebo (*see table 10*).

The primary outcome was exacerbation treated with antibiotics and/or oral corticosteroids, but we also conducted analyses relating treatment with low-dose theophylline to differing levels of treatment for COPD exacerbations, i.e. antibiotics only, oral corticosteroids only or antibiotics and oral corticosteroids (see *Appendix 5, table36*). In the adjusted model, for exacerbations treated with antibiotics only, IRR (95% CI) was 0.94 (0.78, 1.14), for exacerbations treated with oral corticosteroids only 0.88 (0.62, 1.25), and for exacerbations treated with antibiotics and oral corticosteroids 1.02 (0.92, 1.14).



[a] Reasons for ineligibility were as follows: 16 did not meet inclusion criteria for established COPD diagnosis or had predominant respiratory disease other than COPD, 10 had not had 2 exacerbations in previous year, 7 did not meet the smoking history criteria, 7 contraindicated medication, drug interaction 3 were not currently using ICS, 1 was not clinically stable, 2 were participating in another clinical trial, 1 was currently taking theophylline, 1 had known or suspected hypersensitivity to theophylline, 1 pregnancy, 2 with severe heart disease, 11 did not meet two or more of the inclusion criteria.

Figure 4: Consort (intention to treat analysis)

Table 10: Exacerbation outcomes (Intention to treat analysis)

	Theophylline	Placebo		Estimate	Lower CI	Upper CI	p-value
Primary outcome: Exacerbations							
Total number included in analysis	772	764					
Person years follow-up	747.5	742.1					
Number with at least one exacerbation	633	609					
Total number of exacerbations	1727	1703					
Mean number of exacerbations	2.24	2.23	unadjusted IRR	1.00	0.92	1.09	0.965
SD (number of exacerbations)	1.99	1.97	adjusted IRR[a]	0.99	0.91	1.08	0.840
Exacerbations requiring hospital treatment							
Total number included in analysis	772	764					
Person years follow-up	747.5	742.1					
Number with at least one exacerbation	106	130					
Total number of exacerbations	134	185					
Mean number of exacerbations	0.17	0.24	unadjusted IRR	0.72	0.55	0.95	0.021
SD (number of exacerbations)	0.49	0.66	adjusted IRR[a]	0.72	0.55	0.94	0.017
Time to first exacerbation (from randomisation)							
Total number included in analysis[b]	756	753					
Number with at least one exacerbation	617	598					
% with at least one exacerbation	81.6	79.4					
Median time to first exacerbation (days)	219	227	unadjusted HR	1.03	0.92	1.14	0.652
25th percentile (time to first exacerbation (days))	132	116	adjusted HR[a]	1.01	0.90	1.13	0.895
75th percentile (time to first exacerbation (days))	334	337					

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
[b] number in analysis differs to primary outcome as exacerbation onset date was unavailable for 27 participants
CI confidence interval, HR hazard ratio, IRR incident rate ratio, SD standard deviation

Secondary outcome: total number of exacerbations of COPD resulting in hospital admission

In those allocated to low-dose theophylline, 106 (13.7%) participants had at least one exacerbation requiring hospital admission, with 134 hospital admissions in total for the group. For those allocated to placebo, there were 130 (17.0%) participants with at least one exacerbation requiring hospital admission, and 185 admissions in total. A comparison of the proportion with at least one exacerbation requiring hospital admission was not significant at the 5% level (13.7% theophylline vs. 17.0% placebo, p = 0.074). In the adjusted model, the IRR for exacerbations of COPD requiring hospital treatment was 0.72 (0.55, 0.94), suggesting that low-dose theophylline resulted in a reduction in the number of exacerbations requiring hospital admission when compared with placebo (table 10). However, further exploration of the data showed that in the theophylline group only 3 participants had more than 3 exacerbations requiring treatment in hospital (12 exacerbations in total), compared to 13 participants in placebo group having more 3 or more exacerbations requiring hospital treatment. (51 exacerbations in total). Therefore a small excess of participants (10) allocated to placebo who had ≥3 exacerbations requiring treatment in hospital accounted for 39 of the excess 51 admissions in the placebo group (*see table 11*).

Table 11: Number of exacerbations requiring hospital admission

Number of exacerbations requiring hospital admission	**Theophylline** N	%	**Placebo** N	%
0	666	86	634	83
1	84	11	100	13
2	19	2	17	2
3	0	-	5	1
4	3	<1	5	1
5	0	-	2	<1
6	0	-	1	<1
	772		784	

Secondary outcome: time to first exacerbation

The date of onset of the first exacerbation after commencing study medication was not available for 27 of the 1242 participants who had at least one exacerbation, therefore this analysis was based on 1509 in the ITT population (294 no exacerbation, 1215 (80.5%) with exacerbation). In those allocated to theophylline, 617/756 (81.6%) had at least one exacerbation, with median time to first exacerbation of 219 days (7.2 months) after

randomisation. For placebo, there were 598/753 (79.4%) participants with at least one exacerbation, with median time to first exacerbation of 227 days (7.5 months). In a Cox regression analysis, the adjusted HR for time to first exacerbation was 1.01 (0.90, 1.13), suggesting no significant difference between the treatment groups in terms of time to first exacerbation (from point of randomisation) during the 12 month follow-up period (*see table 10*).

Secondary outcome: total number of emergency hospital admissions (non COPD)

Hospital admission data were available for 1517 of the 1536 participants in the ITT population (762 theophylline, 755 placebo). A similar proportion of participants had at least one hospital admission for non-COPD related causes. In the participants allocated to low-dose theophylline this was 10.4% (79/762) compared with placebo 12.2% (92/755). In total, there were 116 hospital admissions for participants allocated to theophylline and 119 for those allocated to placebo. The adjusted IRR (95% CI) was 0.99 (0.71, 1.38), suggesting no significant difference in rate of emergency (unscheduled) hospital admissions between the groups (*see table 12*).

Secondary outcome: mortality (all cause and respiratory related)

There were 33 deaths (from all causes) during the 12 month follow-up period, 19 (2.5%) in participants allocated to low-dose theophylline and 14 (1.8%) in participants allocated to placebo. These deaths were respiratory related for 7 theophylline cases and 8 placebo cases. For theophylline relative to placebo the adjusted hazard ratio (95% CI) for deaths from all causes was 1.38 (0.69, 2.76), and for respiratory related causes 0.85 (0.30, 2.40). Therefore there was no evidence of a significant difference between treatment groups for mortality outcomes (*see table 12*).

Secondary outcome: total number of episodes of pneumonia

In total there were 23 episodes of pneumonia reported during the follow-up, 14 in participants allocated to theophylline and 9 in participants allocated to placebo (1.8% theophylline vs 1.2 % placebo). The proportion of admissions for pneumonia was not found to significant differ between treatment groups ($p = 0.307$). The unadjusted OR was 1.55 (0.67, 3.62), however in light of the small event counts no adjustments were made (*see table 12*).

Table 12: Secondary clinical outcomes (Intention to treat analysis)

	Theophylline	Placebo		Estimate	Lower CI	Upper CI	p-value
Emergency hospital admissions (non-COPD)							
Total number included in analysis	762	755					
Number with ≥1emergency hospital admission	79	92					
Total admissions	116	119					
Mean admission rate	0.15	0.16	unadjusted IRR	0.96	0.69	1.35	0.830
SD admission rate	0.56	0.47	adjusted IRR[a]	0.99	0.71	1.38	0.952
All-cause mortality							
Total number included in analysis	772	764					
Number deceased within 12 months	19	14	unadjusted HR	1.35	0.68	2.69	0.398
% deceased within 12 months	2.5	1.8	adjusted HR[a]	1.38	0.69	2.76	0.369
COPD/Respiratory related mortality							
Total number included in analysis	772	764					
Number deceased within 12 months	7	8	unadjusted HR	0.87	0.31	2.39	0.785
% deceased within 12 months	0.9	1.0	adjusted HR[a]	0.85	0.30	2.40	0.762
Pneumonia							
Total number included in analysis	772	764					
Number with pneumonia	14	9	unadjusted OR	1.55	0.67	3.62	0.307
% with pneumonia	1.8	1.2					

Table 12 (continued): Secondary outcomes (Intention to treat analysis)

	Theophylline	Placebo		Estimate	Lower CI	Upper CI	p-value
Total daily dose ICS							
Total number included in analysis	770	762					
N changed medication from baseline	104	111					
Mean ICS daily dose at end of follow up	1606	1622	unadjusted mean difference	-16.3	-86.8	54.2	0.650
SD ICS daily dose at end of follow up	694	714	adjusted mean difference[a]	-12.4	-81.5	56.6	0.724
Change in daily ICS dose from baseline							
Total number included in analysis	770	762					
Mean change in daily ICS dose from baseline	-57	-58	unadjusted mean difference	1.4	-36.5	39.2	0.943
SD change in daily ICS dose from baseline	346	408	adjusted mean difference[a]	3.6	-34.1	41.3	0.852

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
OR Odd ratio, HR Hazard ratio, CI confidence interval, ICS inhaled corticosteroid, SD standard deviation

Secondary outcome: Total dose of inhaled corticosteroids (ICS)

The total daily dose of ICS at baseline was available for 1532 of the 1536 members of the ITT population (two missing from each treatment group). Mean (SD) total daily beclomethasone equivalent ICS dose at baseline was 1662µg (677) in those allocated to theophylline and 1680 µg (691) in those allocated to placebo. During the 12 month follow-up 215 participants changed their medication, 104 (13.5%) theophylline participants and 111 (14.6%) placebo participants (p = 0.550). Mean (SD) total daily beclomethasone equivalent dose at the end of follow-up was 1606µg (694) in those allocated to theophylline and 1622µg (714) in those allocated to placebo, resulting in an adjusted difference of -12.4µg/day (-81.4, 56.6) for theophylline compared to placebo (*see table 12*). This lower dose at end of follow-up in those taking theophylline was not significantly different from placebo. Both groups showed a slight reduction in total daily dose from baseline to end of follow-up but a comparison of the adjusted mean dose change between treatment groups was not significant (p = 0.852).

Secondary outcome: lung function (% predicted FEV_1 and FVC)

In the ITT analysis lung function was found to be similar between the treatment groups with mean (SD) percent predicted FEV_1 at the end of the 12 month follow-up of 51.5% (20.4) for participants allocated to low-dose theophylline (n = 533) and 52.1% (21.7) for participants allocated to placebo (n = 489). The overall difference in FEV_1 percent predicted (across the 12 month period) was -0.56% (-2.42, 1.30) between the groups. A similar pattern was observed for percent predicted FVC with the overall significant difference of -0.28% (-2.33, 1.76) (*see table 13*).

Secondary outcome: mMRC breathlessness scale

Table 14 details the responses to the mMRC breathlessness scale at baseline, 6m and 12m for each treatment group. The proportion of participants in each category is relatively similar across the groups at each time point. The overall adjusted OR from the mixed effects ordinal logistic regression for theophylline relative to placebo is 1.20 (0.88, 1.63) indicating a slight increase in odds of higher mMRC score in theophylline participants than placebo, but the increase is not significant.

Table 13: Lung function (Intention to treat analysis)

Outcome	Time point		Theophylline	Placebo		Overall mean difference	Lower CI	Upper CI	p-value
% Predicted FEV_1	Baseline	Total N	769	757					
		Mean	51.2	52.3					
		SD	20.1	19.8					
	6 months	Total N	553	539					
		Mean	52.2	53.2					
		SD	20.5	20.9					
	12 months	Total N	533	489					
		Mean	51.5	52.1	unadjusted	-0.57	-2.51	1.36	0.561
		SD	20.4	21.7	Adjusted[a]	-0.56	-2.42	1.30	0.555
% Predicted FVC	Baseline	Total N	767	756					
		Mean	84.3	86.3					
		SD	22.3	23.4					
	6 months	Total N	548	535					
		Mean	83.8	84.5					
		SD	22.8	24.7					
	12 months	Total N	525	486					
		Mean	83.1	82.3	unadjusted	-0.37	-2.50	1.75	0.732
		SD	23.8	25.3	Adjusted[a]	-0.28	-2.33	1.76	0.788

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
CI confidence interval, SD standard deviation, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity

Secondary outcome: COPD assessment test (CAT)

The CAT score was very similar between groups at baseline (*see table 15*) and remained similar throughout the 12 month treatment period, with mean (SD) 21.4 (8.2) for participants allocated to low-dose theophylline (n = 633) and 21.4 (8.6) for placebo (n = 615). A comparison of the profile of the CAT scores across the three time points (0, 6 and 12 months), showed an adjusted difference of 0.01 (-0.65, 0.68), suggesting no significant difference between the groups on the impact of COPD on the participants' lives.

Secondary outcome: Hull Airways Reflux Questionnaire (HARQ)

The HARQ assesses respiratory symptoms associated with airway reflux, and was completed by a subset of participants. Participants for whom HARQ data were available were more likely to be female and younger in age than those that had no HARQ data *(Appendix 5; Table 35)*. Data were available on 199 (26.0%) participants allocated to theophylline and 203 (26.9%) allocated to placebo at baseline. The HARQ scores were very similar between treatment groups throughout the study and at 12 months follow-up; for participants allocated to low-dose theophylline the mean (SD) HARQ score was 24.1 (15.7) based on 184 participants, and for those allocated to placebo 24.2 (15.9) on 172 participants. A comparison of the profiles of HARQ scores across the three time points (0, 6 and 12 months), revealed an adjusted difference of -1.10 (-3.46, 1.26), suggesting no significant difference between the groups in reflux associated respiratory symptoms measured by the HARQ (*see table 15*).

Safety outcomes (safety population)

The safety population comprised all participants who were randomised and included in the study (n = 1567) and initiated their study medication. There were 5/788 (0.6%) theophylline allocated participants who did not initiate medication, and 9/779 (1.2%) in the placebo group. The safety population consisted of 1553 (99.1%) participants (783 theophylline, 770 placebo).

Table 14: mMRC Breathlessness (Intention to treat analysis)

Time-point	mMRC category	Theophylline			Placebo		
Baseline	Not troubled by breathlessness except on strenuous exercise (N, n, %)	767	35	4.6	757	50	6.6
	Short of breath when hurrying or walking up a slight hill (N, n, %)	767	211	27.5	757	218	28.8
	Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace (N, n, %)	767	248	32.3	757	235	31.0
	Stops for breath after walking about 100metres or after a few minutes on level ground (N, n, %)	767	219	28.6	757	201	26.6
	Too breathless to leave house, or breathless when dressing/undressing (N, n, %)	767	54	7.0	757	53	7.0
6 months	Not troubled by breathlessness except on strenuous exercise (N, n, %)	676	42	6.2	655	51	7.8
	Short of breath when hurrying or walking up a slight hill (N, n, %)	676	209	30.9	655	189	28.9
	Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace (N, n, %)	676	197	29.1	655	179	27.3
	Stops for breath after walking about 100metres or after a few minutes on level ground (N, n, %)	676	178	26.3	655	186	28.4
	Too breathless to leave house, or breathless when dressing/undressing (N, n, %)	676	50	7.4	655	50	7.6

Table 14 (continued): mMRC Breathlessness (Intention to treat analysis)

Time-point	mMRC category	Theophylline			Placebo		
12 months	Not troubled by breathlessness except on strenuous exercise (N, n, %)	631	38	6.0	615	52	8.5
	Short of breath when hurrying or walking up a slight hill (N, n, %)	631	186	29.5	615	158	25.7
	Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace (N, n, %)	631	174	27.6	615	182	29.6
	Stops for breath after walking about 100 metres or after a few minutes on level ground (N, n, %)	631	178	28.2	615	167	27.2
	Too breathless to leave house, or breathless when dressing/undressing (N, n, %)	631	55	8.7	615	56	9.1

	Estimate	Lower CI	Upper CI	p-value
unadjusted OR	1.27	0.91	1.76	0.157
adjusted OR[a]	1.20	0.88	1.63	0.244

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
CI confidence interval, OR odds ratio, mMRC modified Medical Research Council

Table 15: Patient reported outcomes (Intention to treat analysis)

Outcome, time point		Theophylline	Placebo		Overall mean difference	Lower CI	Upper CI	p-value
COPD Assessment Test score								
Baseline	Total N	764	756					
	Mean	22.7	22.3					
	SD	7.5	7.9					
6 months	Total N	675	657					
	Mean	21.3	21.1					
	SD	8.1	8.3					
12 months	Total N	633	615					
	Mean	21.4	21.4	unadjusted	0.13	-0.59	0.85	0.715
	SD	8.2	8.6	Adjusted[a]	0.01	-0.65	0.68	0.975
Hull Airways Reflux Questionnaire Score								
Baseline	Total N	199	203					
	Mean	24.9	25.8					
	SD	16.0	14.8					
6 months	Total N	191	188					
	Mean	21.9	22.9					
	SD	15.1	15.7					
12 months	Total N	184	172					
	Mean	24.1	24.2	unadjusted	-0.85	-3.34	1.64	0.504
	SD	15.7	15.9	Adjusted[a]	-1.10	-3.46	1.26	0.359

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
CI confidence interval, COPD Chronic Obstructive Pulmonary Disease, SD standard deviation

Serious adverse events

There were 211 (13.6%) participants who had at least one SAE, with 103/783 (13.2%) in participants allocated to low-dose theophylline and 108/770 (14.0%) in participants allocated to placebo. In total there were 276 SAEs reported in individuals within the safety population, these were balanced between the treatment groups, with 141 in theophylline allocated participants and 135 in placebo participants. SAEs were classified using the system organ classification (SOC) code[95]. *Table 16* details for each SOC code and for each treatment group the number of participants with at least one SAE of that code, and the total number of SAEs of that SOC code. No significant differences were observed in the SAE profile of the two treatment groups. The most common SAE SOC code was for 'cardiac disorders', 2.8% (2.3% theophylline, 3.4% placebo). SAEs with a coding of 'respiratory, thoracic and mediastinal' occurred in 2.5% of participants (2.3% theophylline, 2.7% placebo). A borderline significant higher proportion of participants in the theophylline group (2.7%) reported a gastrointestinal SAE compared to 1.3% in placebo ($p = 0.051$). No pregnancies were reported. Line listings are provided in *Appendix 6*.

Adverse reactions

Information on adverse reactions was available for 1408 of the participants (709 theophylline, 699 placebo), with 648 (46%) suffering at least one adverse reaction (341 theophylline, 307 placebo). There were 1701 adverse reactions in total with 883 in those allocated to low-dose theophylline and 818 in those allocated placebo. *Table 17* presents these adverse reactions in more detail, with total number available for analysis for each adverse reaction, number of participants with at least one adverse reaction of that type and the percentage in each group. The five most common adverse reactions were nausea (10.9% theophylline, 8.0% placebo, $p = 0.059$), insomnia (9.3% theophylline, 8.9% placebo, $p = 0.790$), dizziness (8.1% theophylline, 9.6% placebo, $p = 0.290$), gastro-oesophageal reflux (9.4% theophylline, 7.5% placebo, $p = 0.217$) and headache (9.0% theophylline, 7.7% placebo, $p = 0.383$). In addition, a slightly higher proportion of placebo participants reported tachycardia (3.5%) compared to 1.9% for those allocated theophylline ($p = 0.058$). There were no other observed significant differences in adverse reactions between treatment groups.

Table 16: Serious Adverse Events (Intention to treat analysis)

	Theophylline	Placebo	p-value
Total number included in analysis	783	770	
All SAEs			
Number of participants with at least one SAE	103	108	
% of participants with at least one SAE	13.2	14.0	0.616
Total number of SAEs	141	135	
Infection & infestations			
N of participants with at least one SAE of this type	13	9	
% of participants with at least one SAE of this type	1.7	1.2	0.413
Total number of SAEs of this type	13	9	
Neoplasms benign, malignant and unspecified			
N of participants with at least one SAE of this type	17	11	
% of participants with at least one SAE of this type	2.2	1.4	0.272
Total number of SAEs of this type	18	11	
Blood and lymphatic system disorders			
N of participants with at least one SAE of this type	0	2	
% of participants with at least one SAE of this type	0	0.3	
Total number of SAEs of this type	0	2	
Immune system disorders			
N of participants with at least one SAE of this type	0	0	
% of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Endocrine disorders			
N of participants with at least one SAE of this type	0	0	
% of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Metabolism & nutrition disorders			
N of participants with at least one SAE of this type	1	0	
% of participants with at least one SAE of this type	0.1	0	
Total number of SAEs of this type	2	0	
Nervous system disorders			
N of participants with at least one SAE of this type	11	7	
% of participants with at least one SAE of this type	1.4	0.9	0.361
Total number of SAEs of this type	13	7	

Table 16 (continued): Serious Adverse Events (Intention to treat analysis)

	Theophylline	Placebo	p-value
Psychiatric disorders			
N of participants with at least one SAE of this type	1	2	
% of participants with at least one SAE of this type	0.1	0.3	
Total number of SAEs of this type	1	3	
Eye disorders			
N of participants with at least one SAE of this type	0	0	
% of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Ear & labyrinth disorders			
N of participants with at least one SAE of this type	0	0	
% of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Cardiac disorders			
N of participants with at least one SAE of this type	18	26	
% of participants with at least one SAE of this type	2.3	3.4	0.201
Total number of SAEs of this type	21	29	
Vascular disorders			
N of participants with at least one SAE of this type	5	6	
% of participants with at least one SAE of this type	0.6	0.8	
Total number of SAEs of this type	6	6	
Respiratory, thoracic and mediastinal disorders			
N of participants with at least one SAE of this type	18	21	
% of participants with at least one SAE of this type	2.3	2.7	0.590
Total number of SAEs of this type	19	22	
Hepatobiliary disorders			
N of participants with at least one SAE of this type	2	4	
% of participants with at least one SAE of this type	0.3	0.5	
Total number of SAEs of this type	2	4	
Gastrointestinal disorders			
N of participants with at least one SAE of this type	21	10	
% of participants with at least one SAE of this type	2.7	1.3	0.051
Total number of SAEs of this type	22	12	

Table 16 (continued): Serious Adverse Events (Intention to treat analysis)

	Theophylline	Placebo	p-value
Skin & subcutaneous tissue disorders			
N of participants with at least one SAE of this type	1	0	
% of participants with at least one SAE of this type	0.1	0	
Total number of SAEs of this type	1	0	
Musculoskeletal and connective tissue disorders			
N of participants with at least one SAE of this type	5	9	
% of participants with at least one SAE of this type	0.6	1.2	
Total number of SAEs of this type	5	11	
Renal and urinary disorders			
N of participants with at least one SAE of this type	6	4	
% of participants with at least one SAE of this type	0.8	0.5	
Total number of SAEs of this type	6	4	
Pregnancy, puerperium and perinatal conditions			
N of participants with at least one SAE of this type	0	0	
% of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Reproductive system & breast disorders			
N of participants with at least one SAE of this type	0	0	
% of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Congenital, familial and genetic disorders			
N of participants with at least one SAE of this type	0	0	
% of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
General disorders and administration site disorders			
N of participants with at least one SAE of this type	0	0	
% of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	
Investigations			
N of participants with at least one SAE of this type	0	2	
% of participants with at least one SAE of this type	0	0.3	
Total number of SAEs of this type	0	2	

Table 16 (continued): Serious Adverse Events (Intention to treat analysis)

	Theophylline	Placebo	p-value
Injury, poisoning & procedural complications			
N of participants with at least one SAE of this type	9	13	
% of participants with at least one SAE of this type	1.1	1.7	0.369
Total number of SAEs of this type	11	13	
Surgical and medical procedures			
N of participants with at least one SAE of this type	1	0	
% of participants with at least one SAE of this type	0.1	0	
Total number of SAEs of this type	1	0	
Social circumstances			
N of participants with at least one SAE of this type	0	0	
% of participants with at least one SAE of this type	0	0	
Total number of SAEs of this type	0	0	

SAE serious adverse event

Table 17: Adverse reactions (intention to treat analysis)

Adverse Reaction	Theophylline	Placebo	p-value
Any adverse reaction			
N included in analysis	709	699	
N with at least one adverse reaction	341	307	
% with at least one adverse reaction	48.1	43.9	0.116
Total AR	883	818	
Anaphylactic/anaphylactoid reaction			
N included in analysis	692	679	
N with at least one adverse reaction of this type	0	1	
% with at least one adverse reaction of this type	0.0	0.1	
Hypersensitivity			
N included in analysis	692	679	
N with at least one adverse reaction of this type	5	5	
% with at least one adverse reaction of this type	0.7	0.7	>0.999
Nausea			
N included in analysis	695	679	
N with at least one adverse reaction of this type	76	54	
% with at least one adverse reaction of this type	10.9	8.0	0.059
Reflux			
N included in analysis	693	678	
N with at least one adverse reaction of this type	65	51	
% with at least one adverse reaction of this type	9.4	7.5	0.217
Diarrhoea			
N included in analysis	693	680	
N with at least one adverse reaction of this type	53	46	
% with at least one adverse reaction of this type	7.6	6.8	0.527
Abdominal pain			
N included in analysis	692	679	
N with at least one adverse reaction of this type	42	34	
% with at least one adverse reaction of this type	6.1	5.0	0.390
Gastric irritation			
N included in analysis	691	679	
N with at least one adverse reaction of this type	38	28	
% with at least one adverse reaction of this type	5.5	4.1	0.235

Table 17 (continued): Adverse reactions (intention to treat analysis)

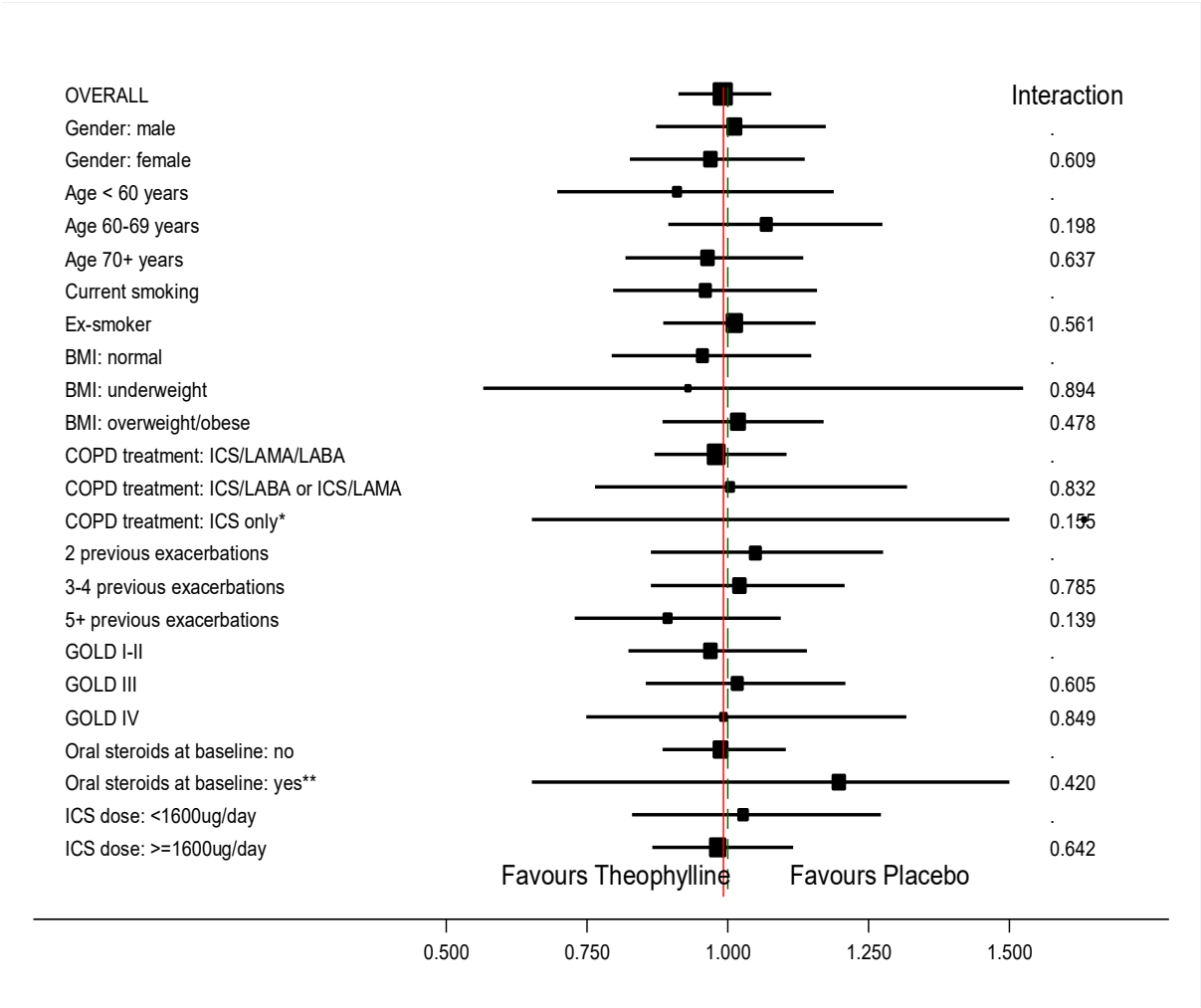
Adverse Reaction	Theophylline	Placebo	p-value
Vomiting			
N included in analysis	693	678	
N with at least one adverse reaction of this type	28	22	
% with at least one adverse reaction of this type	4.0	3.2	0.432
Palpitations			
N included in analysis	690	678	
N with at least one adverse reaction of this type	29	26	
% with at least one adverse reaction of this type	4.2	3.8	0.729
Tachycardia			
N included in analysis	691	678	
N with at least one adverse reaction of this type	13	24	
% with at least one adverse reaction of this type	1.9	3.5	0.058
Insomnia			
N included in analysis	691	678	
N with at least one adverse reaction of this type	64	60	
% with at least one adverse reaction of this type	9.3	8.9	0.790
Anxiety			
N included in analysis	691	679	
N with at least one adverse reaction of this type	52	42	
% with at least one adverse reaction of this type	7.5	6.2	0.327
Rash			
N included in analysis	691	679	
N with at least one adverse reaction of this type	35	27	
% with at least one adverse reaction of this type	5.1	4.0	0.332
Pruritus			
N included in analysis	692	679	
N with at least one adverse reaction of this type	51	63	
% with at least one adverse reaction of this type	7.4	9.3	0.201
Tremor			
N included in analysis	691	678	
N with at least one adverse reaction of this type	34	38	
% with at least one adverse reaction of this type	4.9	5.6	0.571

Table 17 (continued): Adverse reactions (intention to treat analysis)

Adverse Reaction	Theophylline	Placebo	p-value
Headache			
N included in analysis	691	678	
N with at least one adverse reaction of this type	62	52	
% with at least one adverse reaction of this type	9.0	7.7	0.383
Dizziness			
N included in analysis	691	678	
N with at least one adverse reaction of this type	56	66	
% with at least one adverse reaction of this type	8.1	9.7	0.290
Agitation			
N included in analysis	691	679	
N with at least one adverse reaction of this type	22	18	
% with at least one adverse reaction of this type	3.2	2.6	0.558
Convulsions			
N included in analysis	691	678	
N with at least one adverse reaction of this type	2	4	
% with at least one adverse reaction of this type	0.3	0.6	0.448
Hyperuricemia			
N included in analysis	691	678	
N with at least one adverse reaction of this type	9	7	
% with at least one adverse reaction of this type	1.3	1.0	0.803
Diuresis			
N included in analysis	691	678	
N with at least one adverse reaction of this type	49	48	
% with at least one adverse reaction of this type	7.1	7.1	0.993
Urinary retention			
N included in analysis	691	677	
N with at least one adverse reaction of this type	16	15	
% with at least one adverse reaction of this type	2.3	2.2	0.901
Other			
N included in analysis	691	677	
N with at least one adverse reaction of this type	82	86	
% with at least one adverse reaction of this type	11.9	12.7	0.638

Subgroup analysis (intention to treat)

Table 37(*Appendix 5*) details the results of the subgroup analysis for the pre-specified subgroups. Given the exploratory nature of the analyses, we present 99% confidence intervals. *Figure 5* displays this information, alongside the p-value for the interaction in the adjusted model. There was no evidence at the 1% level of statistical significance that any effect of low-dose theophylline differed between subgroups of age, gender, smoking status, BMI, COPD treatments, exacerbation history, COPD severity, baseline ICS dose or use of maintenance oral corticosteroids.



[a] Vertical dotted line represents the line of no effect (IRR = 1), vertical solid line indicates the overall treatment effect for exacerbation (IRR = 0.992).

*Upper limit of CI truncated to 1.5, actual value is 4.09

** Upper limit of CI truncated to 1.5, actual limit is 2.20

Figure 5: Forest plot of estimates from the subgroups[a]

Treatment adherence/compliance

Adherence/compliance was defined as participants having taken ≥ 70% of expected doses of study tablets. Within the ITT population (n = 1536), there were 1180 (76.8%) participants who fulfilled the definition of adherent/compliant (and make up the per-protocol population). Within the theophylline allocated group 181/772 (23.4%) were classed as non-adherent/non-

compliant, with 3 of these never initiating treatment, 171 were non-persistent (i.e. ceased) with study medication and 7 who persisted with study medication, but from returned medication it was evident that they were non-adherent/non-compliant (*see table 18*). In addition, 32/591 of low-dose theophylline participants fulfilled the adherent/compliant definition despite not persisting with study medication, usually very late in the treatment period (*see table 19*). Within the placebo group, 175/764 (22.9%) were classed as non-adherent/non-compliant, with 6 never initiating medication, 159 were non-persistent with study medication and 10 who persisted with study medication but medication returns demonstrated poor implementation (*see table 18*). A further 34 were non-persistent with medication but fulfilled the definition of adherent/compliant because they ceased study medication late into the treatment period (*see table 19*). In summary, the per-protocol population consists of 1180 participants, 591 theophylline and 589 placebo, there were 1146 person years of follow up data (*see table 18*). A comparison of the proportion non-adherent/compliant (23.4% theophylline vs 22.9% placebo) was not significant (p = 0.802). In total 203 of 772 participants in the theophylline arm were non-persistent with medication compared to 193 of 764 in the placebo arm (unadjusted IRR= 1.05 (0.84-1.32)).

Table 18: Compliance information

	Theophylline	**Placebo**
Total N	772	764
Not adherent/ compliant (<70%)[a]	181	175
Did not start medication (non-initiation)	3	6
Actively ceased medication (non-persistence)	171	159
Did not cease (persistent), but adherence/compliance < 70%	7	10
Compliant (>70%)	591	589

[a] unadjusted incident rate ratio 1.03, 95% confidence interval 0.81-1.31, p=0.802

Reasons for stopping medication

Table 19 presents the reasons for stopping medication amongst the ITT population by System Organ Class (SOC) code. The most common reason for stopping medication was for gastrointestinal disorders (46 theophylline, 32 placebo), with surgical and medical procedures second (19 theophylline, 21 placebo), although this included some participants who had discontinued ICS containing inhalers, the majority of this group comprised participants advised to discontinue the study drug by a clinician after presenting with a wide range of

illnesses. In total 46 participants discontinued study medication because they felt no benefit (25 theophylline, 21 placebo) and in 64 cases no reason was given (28 theophylline, 36 placebo), with a further 29 ceasing for social circumstances. There were no obvious differences between the two treatment groups in the reasons why study medication was discontinued, but no formal statistical testing was undertaken.

Table 19: Reasons for stopping medication (of those that started)

	Theophylline	**Placebo**
Total N	772	764
Did not start medication (non-initiation)	3	6
Actively ceased medication (non-persistent)	171	159
Adherent/compliant but ceased medication (non-persistent)	32	34
Total ceasing medication (that started) (non-persistent)[a]	203	193
Reason for stopping medication		
Infections and infestations	2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7	2
Psychiatric disorders	2	4
Nervous system disorders	19	15
Ear and labyrinth disorders	3	3
Cardiac disorders	7	6
Vascular disorders	1	1
Respiratory, thoracic and mediastinal disorders	10	19
Gastrointestinal disorders	46	32
Hepatobiliary disorders	0	1
Skin and subcutaneous tissue disorders	9	7
Musculoskeletal and connective tissue disorders	4	8
Renal and urinary disorders	5	1
Injury, poisoning and procedural complications	1	1
Surgical and medical procedures	19	21
Social circumstances	15	14
Participant felt no benefit	25	21
No reason given	28	36

[a] unadjusted incident rate ratio 1.05, 95% confidence interval 0.84-1.32, p=0.676

Per protocol analysis

The per-protocol population comprised the 1180 participants of the ITT population that met the study definition of adherent with their study medication. The per-protocol analysis comprised 591 participants allocated to low-dose theophylline and 589 allocated to placebo (*figure 6*).

Primary outcome: total number of exacerbations of COPD requiring a change in management

In the per-protocol population, 591 theophylline allocated participants had mean (SD) exacerbations of 2.20 (1.96) compared with 2.14 (1.92) for the 589 placebo participants. In total there were 1298 exacerbations in the theophylline group and 1258 in placebo. The adjusted incidence rate ratio (IRR) and 95% CI for COPD exacerbation was 1.00 (0.91, 1.10), indicating no difference in the exacerbation rate during the 12 month follow-up period for those on low-dose theophylline compared with placebo who were adherent/compliant with study medication (*see table 20*).

Secondary outcome: total number of exacerbations of COPD resulting in hospital admission

In the PP population, 76/591 (13%) participants allocated to theophylline had at least one COPD exacerbation enquiring hospital admission and there were 92 admissions in the group overall. In those allocated to placebo 88/589 (15%) had at least one admission, with 126 admission overall. The mean (SD) number of COPD exacerbations requiring hospital admission was 0.16 (0.45) for the 591 theophylline compliant participants and 0.21 (0.61) for the 589 placebo participants. In the adjusted model, the IRR for COPD exacerbations requiring hospital admission was 0.70 (0.50, 0.97) suggesting a significant reduction in the number of exacerbations requiring hospital admission for the low-dose theophylline compliant group compared to placebo (*see table 20*).

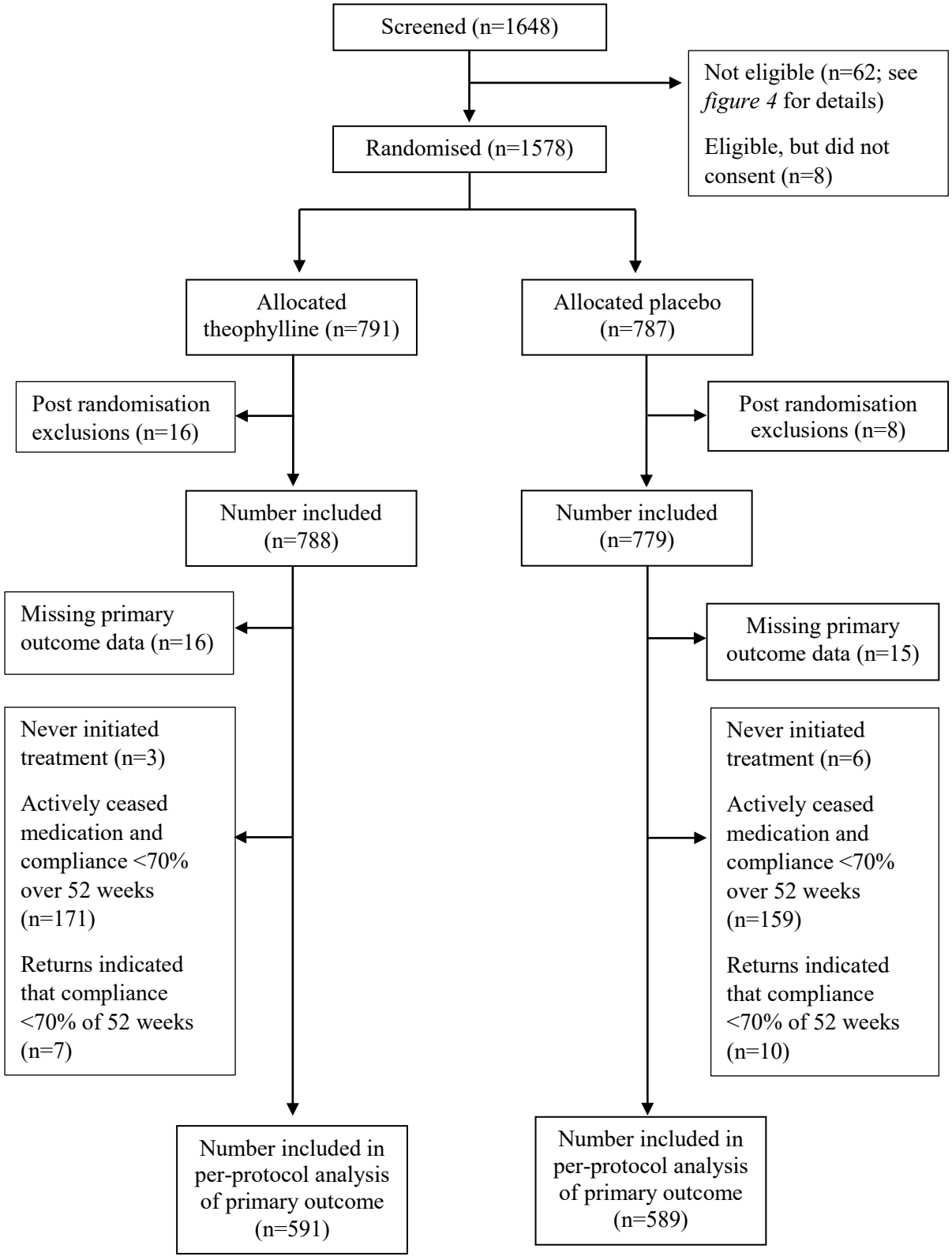


Figure 6: Consort (per-protocol analysis)

Secondary outcome: time to first exacerbation

Time to first exacerbation information was missing for 19 of the 1180 per-protocol participants therefore this analysis was based on 1161 of the PP population. In those allocated to theophylline, 468/578 (81.0%) had at least one exacerbation, with median time to first exacerbation of 221 days (7.3 months) after randomisation. For placebo, there were 459/583 (78.7%) participants with at least one exacerbation, with median time to first exacerbation of 232 days (7.7 months). In a Cox regression analysis, the adjusted HR for time to first exacerbation was 1.02 (0.90, 1.16), suggesting no difference between the treatment groups in terms of time to first exacerbation (from point of randomisation) during the 12 month follow-up period (*see table 20*).

Secondary outcome: total number of emergency hospital admissions (non COPD)

Hospital admission data were available for 1176 /1180 of the per-protocol population. Overall 111 participants had at least one admission (45 theophylline, 66 placebo), with 66 and 85 admissions respectively. The adjusted IRR for admission was 0.82 (0.54, 1.24), suggesting no significant difference in the rate of non-COPD emergency hospital admissions for participants compliant with low-dose theophylline compared to placebo (*see table 21*).

Secondary outcome: mortality (all cause and respiratory related)

There were 22 deaths (from all causes) during the 12 month follow-up period in the per-protocol population, 13 (2.2%) in participants taking theophylline and 9 (1.5%) in participants taking placebo. These deaths were respiratory related for 5 cases in each of the theophylline and placebo groups. The unadjusted hazard ratio (95% CI) for deaths from all causes was 1.45 (0.62, 3.38), and for respiratory related causes 1.00 (0.29, 3.46) for theophylline relative to placebo (*see table 21*). Therefore there was no evidence of a significant difference between treatment groups for mortality outcomes in the per-protocol population. No adjustments were made due to small event counts.

Secondary outcome: total number of episodes of pneumonia

There were 14 episodes of pneumonia with 1.5% (9/591) for low-dose theophylline adherent/compliant participants and 0.9% (5/589) for placebo. The unadjusted IRR was 1.81 (0.60, 5.44) and no adjustments were made due to small event counts (*see table 21*).

Table 20: Exacerbation outcomes (per-protocol analysis)

	Theophylline	Placebo		Estimate	Lower CI	Upper CI	p-value
Primary outcome: Exacerbations							
Total number included in analysis	591	589					
Person years follow-up	572.8	573.8					
Number with at least one exacerbation	481	465					
Total number of exacerbations	1298	1258					
Mean number of exacerbations	2.20	2.14	unadjusted IRR	1.02	0.92	1.13	0.664
SD (number of exacerbations)	1.96	1.92	adjusted IRR[a]	1.00	0.91	1.10	0.934
Exacerbations requiring hospital admission							
Total number included in analysis	591	589					
Number with at least one exacerbation	76	88					
Total number of exacerbations	92	126					
Mean number of exacerbations	0.16	0.21	unadjusted IRR	0.74	0.53	1.03	0.072
SD (number of exacerbations)	0.45	0.61	adjusted IRR[a]	0.70	0.50	0.97	0.031
Time to 1st exacerbation (from randomisation)							
Total number included in analysis[b]	578	583					
Number with at least one exacerbation	468	459					
% with at least one exacerbation	81.0	78.7					
Median time to first exacerbation (days)	221	232	unadjusted HR	1.04	0.91	1.18	0.576
25th percentile (time to first exacerbation (days))	132	126	adjusted HR[a]	1.02	0.90	1.16	0.733
75th percentile (time to first exacerbation (days))	341	339					

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
[b] Number included is reduced due to date of onset of first exacerbation being missing for 19 participants. CI confidence interval, IRR incident rate ratio, HR hazard ratio, SD standard deviation

Table 21: Secondary clinical outcomes (per-protocol analysis)

	Theophylline	Placebo		Estimate	Lower CI	Upper CI	p-value
Emergency hospital admissions (non-COPD)							
Total number included in analysis	587	589					
N with at least one emergency hospital admission	45	66					
Total admissions	66	85					
Mean admission rate	0.11	0.14	unadjusted IRR	0.77	0.51	1.17	0.220
SD admission rate	0.49	0.45	adjusted IRR[a]	0.82	0.54	1.24	0.351
All-cause mortality							
Total number included in analysis	591	589					
N deceased within 12 months	13	9	unadjusted HR	1.45	0.62	3.38	0.394
% deceased within 12 months	2.2	1.5					
Respiratory related mortality							
Total number included in analysis	591	589					
N deceased within 12 months	5	5	unadjusted HR	1.00	0.29	3.46	0.998
% deceased within 12 months	0.9	0.9					
Pneumonia							
Total number included in analysis	591	589					
Number with pneumonia	9	5	unadjusted OR	1.81	0.60	5.44	0.291
% with pneumonia	1.5	0.9					

Table 21 (continued): Secondary clinical outcomes (per-protocol analysis)

	Theophylline	Placebo		Estimate	Lower CI	Upper CI	p-value
Total daily dose ICS							
Total number included in analysis	589	588					
N changed medication from baseline	78	93					
Mean ICS daily dose at end of follow up	1617	1605	unadjusted mean difference	12.2	-67.6	92.1	0.764
SD (ICS daily dose at end of follow up)	693	704	adjusted mean difference[a]	12.5	-65.9	90.9	0.754
Change in daily ICS dose from baseline							
Total number included in analysis	589	588					
Mean change in daily ICS dose from baseline	-62	-60	unadjusted mean difference	-1.60	-45.4	42.3	0.943
SD (change in daily ICS dose from baseline)	347	417	adjusted mean difference[a]	-0.58	-44.3	43.1	0.979

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
HR hazard ratio, ICS inhaled corticosteroid, IRR incident rate ratio, OR odds ratio, SD standard deviation

Secondary outcome: total dose of ICS

The total daily dose of ICS at baseline was available for 1176 of the 1180 members of the per-protocol population. During the 12 month follow-up 171 participants changed their medication, 78 (13.2%) theophylline participants and 93 (15.8%) placebo participants (p = 0.210). Mean (SD) total daily beclomethasone equivalent dose at the end of follow-up was 1617µg (693) in those allocated to theophylline and 1605µg (704) in those allocated to placebo, resulting in an adjusted daily beclomethasone equivalent difference of 12.5µg (-65.9, 90.9) higher for theophylline compared to placebo (*see table 21*). This higher dose at end of follow-up in those taking theophylline was not significantly different from placebo. Both groups showed a slight reduction in total daily dose from baseline to end of follow-up but a comparison of the adjusted mean dose change between treatment groups was not significant (p = 0.979).

Secondary outcome: lung function (% predicted FEV_1 and FVC)

In the per-protocol analysis of lung function the profile was found to be similar between the treatment groups with mean (SD) percent predicted FEV_1 at the end of the 12 month follow-up of 51.3% (20.3) for the theophylline compliant participants (n=455) and 52.6% (21.8) for placebo (n=432). The overall difference (across the 12 month period) was -1.33% (-3.47, 0.80), between the groups, with theophylline adherence/compliance showing a slight (non-significant) reduction compared to placebo (*see table 22*). A similar pattern was observed for percent predicted FVC with an overall difference of -0.65% (-2.96, 1.67). This was a larger reduction than that observed in the ITT analysis, but remained non-significant.

Secondary outcome: mMRC breathlessness scale

Table 23 details the responses to the mMRC breathlessness scale at baseline, 6m and 12m for each treatment group in the per-protocol population. In the unadjusted model the OR for higher mMRC in theophylline participants compared to placebo is 1.54 (1.05, 2.26), and adjusted 1.39 (0.97, 1.98).

Table 22: Lung function (per-protocol analysis)

Outcome	Time point		Theophylline	Placebo		Overall mean difference	Lower CI	Upper CI	p-value
% Predicted FEV_1	Baseline	Total N	588	583					
		Mean	50.7	52.8					
		SD	20.5	20.0					
	6 months	Total N	471	471					
		Mean	52.0	53.7					
		SD	20.8	20.8					
	12 months	Total N	455	432					
		Mean	51.3	52.6	unadjusted	-1.41	-3.65	0.82	0.215
		SD	20.3	21.8	Adjusted[a]	-1.33	-3.47	0.80	0.221
% Predicted FVC	Baseline	Total N	586	582					
		Mean	84.2	86.6					
		SD	22.9	23.5					
	6 months	Total N	467	467					
		Mean	84.3	84.6					
		SD	23.0	24.3					
	12 months	Total N	449	431					
		Mean	83.3	82.6	unadjusted	-0.84	-3.25	1.56	0.492
		SD	23.2	25.3	Adjusted[a]	-0.65	-2.96	1.67	0.584

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.SD standard deviation, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, CI confidence interval

Table 23: mMRC Breathlessness (per-protocol analysis)

Time-point	mMRC category [75]	Theophylline			Placebo		
Baseline	Not troubled by breathlessness except on strenuous exercise (N, n, %)	586	26	4.4	584	44	7.5
	Short of breath when hurrying or walking up a slight hill (N, n, %)	586	160	27.3	584	176	30.1
	Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace (N, n, %)	586	198	33.8	584	181	31.0
	Stops for breath after walking about 100metres or after a few minutes on level ground (N, n, %)	586	157	26.8	584	149	25.5
	Too breathless to leave house, or breathless when dressing/undressing (N, n, %)	586	45	7.7	584	34	5.8
6 months	Not troubled by breathlessness except on strenuous exercise (N, n, %)	560	34	6.1	552	46	8.3
	Short of breath when hurrying or walking up a slight hill (N, n, %)	560	182	32.5	552	160	29.0
	Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace (N, n, %)	560	161	28.8	552	155	28.1
	Stops for breath after walking about 100metres or after a few minutes on level ground (N, n, %)	560	142	25.4	552	153	27.7
	Too breathless to leave house, or breathless when dressing/undressing (N, n, %)	560	41	7.3	552	38	6.9

Table 23 (continued): mMRC Breathlessness (per-protocol analysis)

Time-point	mMRC category	Theophylline			Placebo		
12 months	Not troubled by breathlessness except on strenuous exercise (N, n, %)	535	32	6.0	527	47	8.9
	Short of breath when hurrying or walking up a slight hill (N, n, %)	535	167	31.2	527	149	28.3
	Walks slower than contemporaries on level ground or has to stop for breath when walking at own pace (N, n, %)	535	146	27.3	527	153	29.0
	Stops for breath after walking about 100metres or after a few minutes on level ground (N, n, %)	535	147	27.5	527	135	25.6
	Too breathless to leave house, or breathless when dressing/undressing (N, n, %)	535	43	8.0	527	43	8.2

	Estimate	Lower CI	Upper CI	p-value
unadjusted OR	1.54	1.05	2.26	0.028
adjusted OR[a]	1.39	0.97	1.98	0.074

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
CI confidence interval, OR odds ratio

Secondary outcome: COPD assessment test (CAT)

CAT scores were very similar between treatment groups at baseline (*see table 24*) and remained similar through to 12 months, with a mean (SD) score of 21.0 (8.2) for theophylline adherent/compliant participants (n = 534) and 20.9 (8.7) for placebo (n = 527) in the per-protocol population. A comparison of the profile of the CAT score across the three time points (0, 6 and 12 months), showed an adjusted difference of 0.29 (-0.45, 1.04), suggesting no significant difference between the groups of the per-protocol population on the impact of COPD on the participants' lives.

Secondary outcome: HARQ

At 12 months, the mean (SD) HARQ score was 23.0 (15.6) in 153 theophylline adherent/compliant participants and 24.4 (15.8) in 141 placebo adherent/compliant participants. A comparison of the profile of the HARQ scores across the three time points (0, 6 and 12 months), showed an adjusted difference of -1.62 (-4.25, 1.01), suggesting no significant difference between the per-protocol treatment groups in reflux associated respiratory symptoms measured by the HARQ (*see table 24*).

Sensitivity analysis

We undertook a sensitivity analysis for the primary outcome and a number of secondary outcomes that excluded the 33 participants who died during the 12 month follow up period. This left 1503 participants of the ITT population, 753 theophylline and 750 placebo. *Supplementary tables 38 and 39 (Appendix 5)* give the detail for these analyses.

Primary outcome

After excluding participants who died the adjusted IRR for COPD exacerbations was 0.99 (0.91, 1.07), (*Appendix 5, table 38*) indicating that restricting the result to only those who were alive for the full 12 month follow-up did not change the result of the original ITT analysis (0.99 (0.91, 1.08)).

Secondary outcomes – hospital admissions

Excluding the 33 deaths from the analysis for COPD exacerbations requiring hospital admission, the adjusted IRR was 0.73 (0.55, 0.97) in the remaining 1503 members of the ITT population, which is very similar to the treatment estimate observed for all 1536 members of the ITT population (0.72 (0.55, 0.94)). For admission to hospital for non-COPD reasons, data were available for 1485 people after excluding the deaths. The adjusted IRR for admission for theophylline relative to placebo was 1.03 (0.73, 1.43) compared to 0.99 (0.71, 1.38) in the full ITT population.

Secondary outcomes - other

Excluding the 33 deaths made very little difference to the estimates of treatment effect for lung function (FEV_1 or FVC) or the patient reported outcomes of CAT and HARQ (*Appendix 5, table 39*). For FEV_1 the adjusted difference was -0.58% (-2.46, 1.29) compared with -0.56% (-2.42,

1.30) and for FVC -0.37% (-2.43, 1.69) compared with -0.28% (-2.33, 1.76) for the ITT population. For the CAT score, the treatment difference was 0.02 (-0.65, 0.69) compared with 0.01 (-0.65, 0.69) in the original ITT population. The HARQ analysis gave -0.88 (-3.27, 1.51) compared with -1.10 (-3.46, 1.26) of the original ITT population. In summary excluding the 33 deaths made little or no difference to the estimates of treatment effect within the ITT population.

Summary

In summary, there was no evidence that overall low-dose theophylline significantly reduced the number of COPD exacerbations requiring treatment compared to placebo. There was some evidence that low-dose theophylline reduced exacerbations that required hospital admission with most benefit being evident in a small 1% (13/1556) sub-group of patients frequently hospitalised with COPD. Total number of emergency hospital admissions (non COPD) did not significantly differ between groups, and neither did total episodes of pneumonia or mortality. Lung function was similar across the 12 month follow-up in the two groups. Impact of disease on patients measured by CAT, mMRC breathlessness scale and HARQ showed no significant differences. The safety profile of low-dose theophylline was similar to placebo. There was no evidence that the treatment effect differed in any of the pre-specified sub groups.

Table 24: Patient reported outcomes (per-protocol analysis)

Time point		Theophylline	Placebo		Overall mean difference	Lower CI	Upper CI	p-value
COPD Assessment Test Score								
Baseline	Total N	584	583					
	Mean	22.7	21.8					
	SD	7.5	7.9					
6 months	Total N	560	555					
	Mean	21.0	20.5					
	SD	8.2	8.2					
12 months	Total N	534	527					
	Mean	21.0	20.9	unadjusted	0.52	-0.29	1.33	0.212
	SD	8.2	8.7	Adjusted[a]	0.29	-0.45	1.04	0.444
Hull Airways Reflux Questionnaire Score								
Baseline	Total N	153	152					
	Mean	25.2	26.8					
	SD	15.9	14.7					
6 months	Total N	160	151					
	Mean	21.2	22.5					
	SD	14.8	15.6					
12 months	Total N	153	141					
	Mean	22.9	24.4	unadjusted	-1.39	-4.17	1.40	0.329
	SD	15.6	15.8	Adjusted[a]	-1.62	-4.25	1.01	0.227

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
CI confidence interval, COPD Chronic Obstructive Pulmonary Disease, SD standard deviation

CHAPTER 5 – COST EFFECTIVENESS

This chapter reports the health economics results from the trial. The objectives of the health economics section was to determine the cost-effectiveness of adding low dose theophylline to ICS therapy over a 12-month period. Mean resource use per participant is presented, along with levels of missing data and mean unadjusted and adjusted costs.

Baseline resource use and costs

Baseline resource use and costs are presented in *table 25*.

Table 25: Baseline resource use and costs (per participant)

	Theophylline Mean (SD)	**Placebo Mean (SD)**
RESOURCE USE		
Exacerbations		
Number of exacerbations requiring treatment in previous 12 months	3.63 (2.22) n=772	3.52 (2.08) n=764
Exacerbations resulting in hospitalisation in previous 12 months	0.404 (0.840) n=768	0.358 (0.918) n=758
Non-exacerbation resource use (Mean number of uses per participant in 6 months prior to randomisation)		
COPD maintenance treatment at baseline	n=769	n=758
Inhaled short acting beta 2 agonist	0.967 (0.177)	0.972 (0.164)
Inhaled combined ICS LABA	0.966 (0.181)	0.960 (0.195)
Inhaled short acting muscarinic antagonist	0.068 (0.251)	0.065 (0.246)
Inhaled ICS	0.043 (0.203)	0.040 (0.195)
Inhaled non-combination LABA	0.018 (0.134)	0.029 (0.168)
Inhaled LAMA	0.805 (0.397)	0.817 (0.387)
Nebulised ipratropium	0.051 (0.291)	0.041 (0.246)
Nebulised short acting beta 2 agonist	0.204 (0.536)	0.185 (0.491)
Oral mucolytics	0.247 (0.432)	0.248 (0.432)
Oral leukotriene antagonists	0.042 (0.200)	0.041 (0.198)
Long-term antibiotics	0.066 (0.249)	0.059 (0.236)
Regular medication		
Count[a]	4.65 (3.64) n=772	4.41 (3.54) n=764

Table 25 (continued): Baseline resource use and costs (per participant)

	Theophylline Mean (SD)	Placebo Mean (SD)
COSTS[b]		
Baseline COPD maintenance treatment costs[c]	n=769	n=758
Inhaled short acting beta 2 agonist	£17.5 (£3.2)	£17.60 (£3.0)
Inhaled combined ICS LABA	£325.00 (£1,897)	£247.00 (£486)
Inhaled short acting muscarinic antagonist	£2.77 (£10.3)	£2.64 (£10.1)
Inhaled ICS	£7.28 (£50.8)	£8.27 (£71.2)
Inhaled non-combination LABA	£3.89 (£28.6)	£6.20 (£35.9)
Inhaled LAMA	£164.00 (£80.9)	£167.00 (£79.0)
Nebulised ipratropium	£4.78 (£26.3)	£4.19 (£24.0)
Nebulised short acting beta 2 agonist	£8.55 (£21.3)	£8.14 (£20.4)
Oral mucolytics	£34.70 (£60.7)	£34.90 (£60.8)
Oral leukotriene antagonists	£0.44 (£2.10)	£0.43 (£2.08)
Long-term antibiotics	£21.00 (£88.0)	£25.70 (£275)
Total baseline COPD maintenance treatment costs	£590.00 (£1,904)	£522.00 (£571)

[a] Count (medication); mean number of non-COPD medications taken by each participant.

[b] Baseline resource use was collected for current use of COPD maintenance treatment and regular medication. For calculating baseline resource use and costs we have assumed this usage to be for the six months prior to baseline.

[c] Baseline costs are calculated for the previous 6 months based on the medications used at baseline.

COPD chronic obstructive pulmonary disease, ICS inhaled corticosteroid, LABA long-acting beta-agonist, LAMA long-acting muscarinic antagonists, n number of participants, SD standard deviation

There is no significant difference between arms for any of these baseline resources.

Resource use

Table 26 reports the mean resource use per participant for complete cases, during the 12 month follow-up period.

As discussed in the previous chapter the treatment of exacerbations at hospital was significantly different between groups; there were more exacerbations treated in hospital in the placebo group than the theophylline group (p=0.02).

Table 26: 12 month resource use for complete cases (per participant)

	Theophylline Mean (SD)	**Placebo Mean (SD)**
	n=743	n=727
Intervention		
Theophylline	1	0
Exacerbation resource use[a]		
(Mean number of uses per participant in 12 month follow-up period)		
Increased use of short acting beta 2 agonist	1.01 (1.51)	1.04 (1.60)
Increased/started nebulised bronchodilator	0.288 (0.836)	0.318 (0.910)
Oral corticosteroid	1.72 (1.87)	1.68 (1.79)
Antibiotics	2.01 (1.83)	2.01 (1.84)
Oxygen	0.129 (0.511)	0.142 (0.541)
Other	0.075 (0.320)	0.076 (0.354)
Treated at home	2.08 (1.92)	2.10 (1.90)
Care by services to prevent hospitalisation	0.086 (0.379)	0.100 (0.416)
Admitted to hospital	0.179 (0.497)	0.253 (0.676)
Non-exacerbation resource use		
COPD maintenance treatment		
(Mean number of uses per participant in 12 month follow-up period)		
Inhaled short acting beta 2 agonist	0.926 (0.262)	0.934 (0.248)
Inhaled combined ICS LABA	0.918 (0.275)	0.922 (0.269)
Inhaled short acting muscarinic antagonists	0.069 (0.253)	0.062 (0.241)
Inhaled ICS	0.039 (0.194)	0.044 (0.205)
Inhaled non-combination LABA	0.032 (0.177)	0.047 (0.211)
Inhaled LAMA	0.817 (0.387)	0.824 (0.381)
Nebulised ipratropium	0.046 (0.209)	0.037 (0.189)
Nebulised short acting beta 2 agonist	0.157 (0.364)	0.176 (0.381)
Oral mucolytics	0.285 (0.452)	0.294 (0.456)
Oral leukotriene antagonists	0.046 (0.209)	0.044 (0.205)
Long-term antibiotics	0.092 (0.289)	0.085 (0.279)

Table 26 (continued): 12 month resource use for complete cases (per participant)

	Theophylline Mean (SD)	Placebo Mean (SD)
Non-exacerbation health services use		
Inpatient services		
General medical ward stays (number of stays)	0.059 (0.263)	0.084 (0.406)
Long stay ward stays (number of stays)	0.004 (0.063)	0 (0)
Other inpatient services (number of contacts)	0.027 (0.192)	0.022 (0.173)
Out-patient		
Hospital day-case admissions (number of admissions)	0.187 (0.900)	0.169 (0.530)
Hospital out-patient appointments (number of appointments)	1.68 (2.63)	1.58 (2.66)
Accident & Emergency (no overnight admission; number of visits)	0.137 (0.490)	0.128 (0.513)
Other inpatient services (number of admissions)	0.514 (2.87)	0.476 (2.23)
Primary care services		
Emergency GP visit	1.03 (1.97)	1.01 (2.10)
Routine GP visit	3.18 (4.33)	2.84 (3.83)
Community district nurse (number of appointments)	0.801 (9.64)	0.631 (3.50)
Hospital at home team (number of contacts)	0.101 (1.01)	0.158 (2.92)
Other primary care services (number of contacts)	2.16 (5.37)	1.77 (3.68)
Non-COPD emergency hospital admissions		
Emergency hospital admissions	0.150 (0.555)	0.158 (0.468)
Regular medication count		
Regular medication count [b]	4.34 (3.55)	4.32 (3.51)

[a] mean number of times each treatment was used for exacerbations per participant

[b] Count (medication); mean number of non-COPD medications taken by each participant

COPD chronic obstructive pulmonary disease, GP general practitioner, ICS inhaled corticosteroid, LABA long-acting beta-agonist, LAMA long-acting muscarinic antagonists, n number of participants, SD standard deviation

Missing data

The disaggregated level of missing data affecting resource use is reported below, these are broken down into exacerbations, maintenance COPD treatment and non-COPD emergency hospital admissions.

Exacerbations (length of exacerbation, treatment costs and location of treatment), 3,430 exacerbations were recorded in total

- 329 participants had missing length of exacerbation data (5.9% missing data points).
- 210 recorded exacerbations were missing location of treatment marker (3.4% missing data points).
- 46 participants with exacerbations treated in hospital had missing lengths of stay.
- 171 recorded exacerbations were missing a treatment cost (1% missing data points).

Maintenance COPD treatment

- 82 participants had missing total COPD maintenance costs (5.6% missing data points), this missing data were replaced with a treatment specific mean.

Non-COPD emergency hospital admissions, 235 non-COPD emergency hospital admissions were recorded

- 9 participants had missing length of stays for emergency hospital admissions (2.8% missing data points).

All missing resource data were replaced using pragmatic, naïve methods suitable for use when missing data is less than 10%.

Table 27 presents the missing economic data for resource use and EQ-5D-3L completion.

Resource use was available for 743 participants in the theophylline arm and 727 in the placebo arm; 29 (3.8%) participants did not have resource use data captured during the follow-up period in the theophylline arm, 37 (4.8%) participants did not have 12 months resource use in the placebo arm. Overall, there were 66 (4.3%) participants missing resource use data for the whole 12 month follow-up period.

The number of participants with missing EQ-5D-3L data was 137 (17.7%) in the theophylline arm and 156 (20.4%) in the placebo arm. Overall there were 293 (19.1%) missing EQ-5D-3L questionnaires.

Table 27: Missing resource use and EQ-5D-3L data

	Theophylline n (%)	Placebo n (%)	Total
Cost data			
Intention to treat population	772 (100%)	764 (100%)	1,536 (100%)
No resource use captured during follow-up	29 (3.8%)	37 (4.8%)	66 (4.3%)
Complete cases	743 (96.2%)	727 (95.2%)	1,470 (95.7%)
EQ-5D-3L data			
Intention to treat population	772 (100%)	764 (100%)	1,536 (100%)
Missing EQ-5D-3L at baseline/6 months or 12 months	137 (17.7%)	156 (20.4%)	293 (19.1%)
Complete cases	635 (82.3%)	608 (79.6%)	1,243 (80.9%)

EQ-5D-3L EuroQoL 5 dimension, 3 level

Costs

Table 28 reports complete case costs (unadjusted). Differences between arms are calculated using a GLM model with identity link, gamma family and a cluster for centre number. Regular medication was not included in these costs due to there being no significant difference between arms in regular medication count.

There is a significant difference of £452 (95% CI £133 to £771) in the mean total costs between arms; placebo being more costly than theophylline. This difference is driven by the difference in exacerbation mean costs between arms; £447 (95% CI £186 to £709) higher in the placebo arm. The difference in exacerbation costs is driven by the location of treatment of exacerbation. The mean difference in location of exacerbation treatment costs is £422 (95% CI £171 to £673) higher in the placebo arm than the theophylline arm. As presented in chapter 4, this is driven by a higher number of exacerbations treated in hospital in the placebo arm than in the theophylline arm. This is reflected in the health economics analysis when location of treatment costs are broken down further into: 'treatment at home', 'care by services to prevent hospitalisation' and 'admitted to hospital'. In 'treatment at home' and 'care by services to prevent hospitalisation' resource use costs there are no significant differences between arms, however, 'admitted to hospital' is £416 (95% CI £177 to £655) higher in the placebo arm compared to the theophylline arm, a statistically significant result.

Table 28: Complete case costs (unadjusted)

	Theophylline mean (SD)	**Placebo mean (SD)**	**Difference**	**95% CI**
Intervention costs	£22 (£0.24)	£0	£22	£22 to £22
Exacerbation costs				
Total exacerbation costs	£585 (£1,682)	£1,033 (£3,383)	-£447	-£709 to -£186
Total location costs	£535 (£1,594)	£958 (£3,185)	-£422	-£673 to -£171
Location - home	£67 (£61)	£68 (£60)	-£1	-£6 to £4
Location - services	£33 (£145)	£38 (£159)	-£5	-£23 to £12
Location - hospital	£436 (£1,538)	£852 (£3,142)	-£416	-£655 to -£177
Treatment	£50 (£167)	£75 (£296)	-£25	-£41 to -£8
Non-exacerbation costs				
Maintenance COPD treatment	£974 (£379)	£978 (£416)	-£4	-£45 to £38
Health services resource use (not exacerbation related)	£819 (£1,224)	£862 (£1,812)	-£43	-£175 to £89
Non-COPD related emergency hospital admissions	£282 (£1,529)	£262 (£1,136)	£20	-£102 to £143
Total costs	£2,684 (£2,882)	£3,136 (£4,851)	-£452	-£771 to -£133
Non-intervention, non-exacerbation costs	£2,075 (£2,079)	£2,101 (£2,528)	-£26	-£234 to £181

CI confidence interval, COPD Chronic Obstructive Pulmonary Disease, SD standard deviation

At a per exacerbation level this difference can be explored further. The mean cost per exacerbation treated in hospital is £3,613 (SE £342) in the placebo arm and £2,671 (SE £220) in the theophylline arm, a significant difference of £941 (SE £386) (95% CI £140 to £1,743). The ten most costly observations (over £10,000) were all in the placebo arm, and were the result of hospital stays of greater than 40 days. Due to the lack of treatment effect we believe this difference to be a chance finding and not a real result of the trial. The distribution for length of hospital stay is similar for both arms apart from a small excess of participants in the placebo arm with longer stays. It is important to note that the proxy for hospital length of stay is length of exacerbation and that this is likely to over-estimate length of stay in hospital. In total, 319 exacerbations were treated in hospital, 185 in the placebo arm and 134 in the theophylline arm.

The treatment of exacerbations had a significant difference between arms of £25 mean cost per participant, less expensive in the theophylline arm. At a per exacerbation level this is driven by treatment with oxygen. The difference in oxygen use per exacerbation using oxygen is £141 (SE £52) (95% CI £40 to £243); less expensive in the theophylline arm than placebo arm. The difference in oxygen treatment is driven by a small number of participants with duration of oxygen treatment greater than 51 days. Seven participants have oxygen treatment duration greater than 51 days, resulting in costs per exacerbation of greater than £1,000 and six of these participants are in the placebo arm.

The wide standard deviations for hospitalised exacerbations, treatment of exacerbations, non-COPD emergency hospital admissions and other health services use indicate a wide range of individual participant's costs within these resource groups.

No other resource use costs are significantly different between arms, which is reflected in no difference between arms for the non-intervention, non-exacerbation costs presented in *table 28*.

Economic outcome

Complete case EQ-5D-3L data and QALYs are reported in *table 29*.

Table 29: Complete case EQ-5D-3L utilities and QALYs for 12 month trial period

	Theophylline Mean (SD)	**Placebo Mean (SD)**	**Difference (95% CI)**
Baseline	0.629 (0.280)	0.643 (0.279)	-0.014 (-0.045 to 0.017)
6 months	0.630 (0.296)	0.642 (0.295)	-0.012 (-0.045 to 0.021)
12 months	0.622 (0.292)	0.623 (0.308)	-0.001 (-0.034 to 0.032)
QALYs over 12 months[a]	0.626 (0.259)	0.637 (0.263)	-0.011 (-0.040 to 0.018)

[a] There were 33 deaths in the ITT population, these participants had QALYs allocated to them for the period they were alive, on a monthly basis.

CI confidence interval, EQ-5D-3L EuroQoL 5 dimension, 3 level, QALY quality adjusted life year, SD standard deviation

Utilities from the EQ-5D-3L at baseline, 6 and 12 month follow-up and QALYs are higher in the placebo arm than the theophylline arm, however, this difference is not significant.

Multiple imputation

Multiple imputation results are presented in *table 30* for costs and QALYs.

Table 30: Multiple imputation results (unadjusted)

	Theophylline Mean (SE)	**Placebo Mean (SE)**	**Difference (95% CI)**
Total costs	£2,702 (£110)	£3,141 (£148)	-£439 (-£846 to -£32)
Total QALYs	0.617 (0.010)	0.621 (0.010)	-0.004 (-0.031 to 0.024)

CI confidence interval, QALY quality adjusted life year, SE standard error

Multiple imputation results mirror the complete case results, with costs significantly higher in the placebo arm, a difference of £439. Total QALYs are higher in the placebo arm, however this is not a statistically significant result, a difference of 0.004.

Bootstrapping

To explore the robustness of these results, 1,000 non-parametric bootstrapped samples were taken from the observed data. The results were plotted using a cost-effectiveness plane to illustrate the mean differences between the arms in incremental costs and QALYs.

Non-adjusted bootstrapped results are presented in *figure 7*. This cost-effectiveness plane clearly illustrates that the majority of total mean costs are less in the theophylline than the placebo arm, with the majority of incremental samples falling in the south-east and south-west quadrants of the cost-effectiveness plane (below the horizontal axis of £0). The majority of total mean QALYs are less in the theophylline arm than the placebo arm, represented by the majority of bootstrapping samples falling in the south-west quadrant where the placebo arm has higher mean QALYs than the theophylline arm. The cost-effective plane includes an ellipse to illustrate the 95% confidence level.

This uncertainty is explored further using cost-effectiveness acceptability curves.

The unadjusted bootstrapped results are presented in *figure 8*. At a willingness to pay of £20,000 there is a 75% chance of theophylline being cost-effective. At £30,000 there is a 64% of theophylline being cost-effective. However, this should be viewed with caution as

there is no significant difference in QALYs or clinical effect, and the difference in costs is driven by a very small number of participants with prolonged hospital admissions and the likelihood that the finding of a difference between arms for exacerbations treated in hospital is a chance finding. Moreover as discussed below the cost benefits of theophylline are not evident in multivariate models.

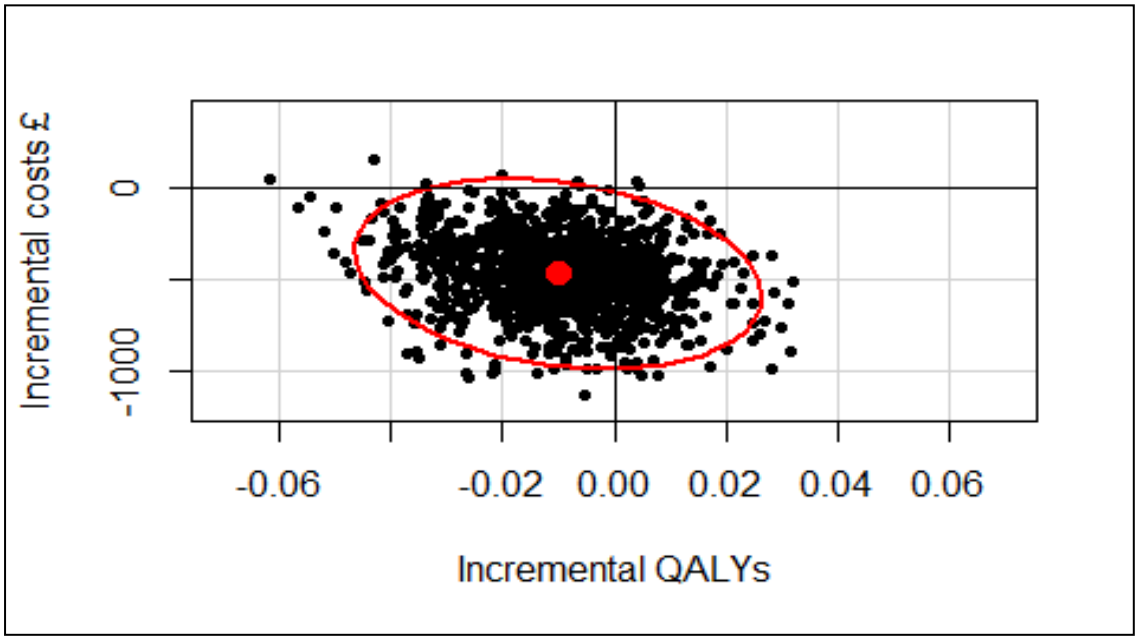


Figure 7: Cost-effectiveness plane (unadjusted)

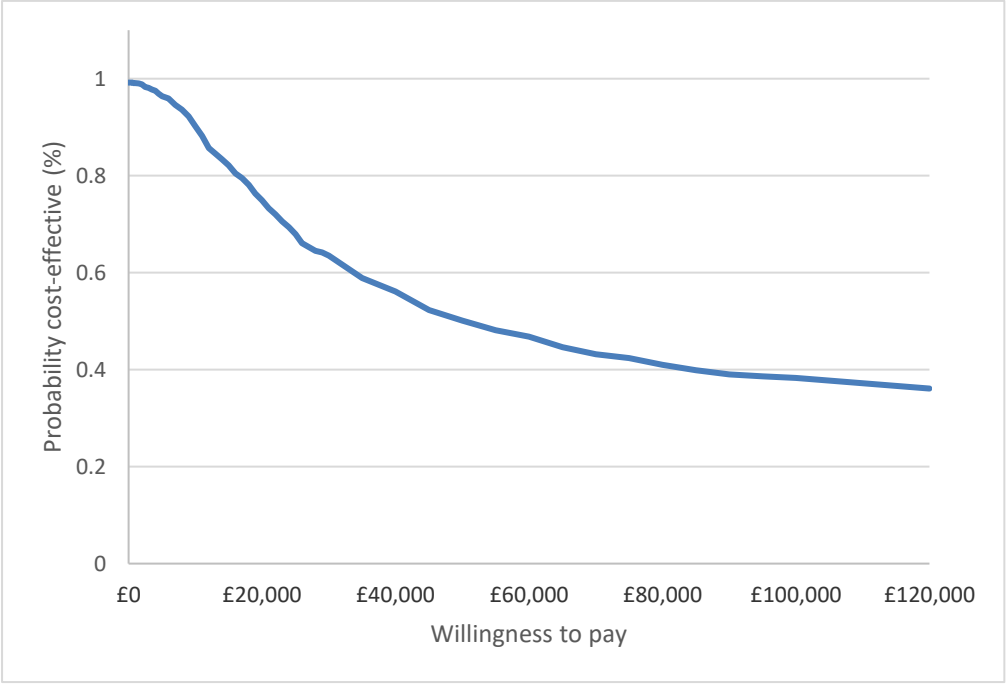


Figure 8: Cost-effectiveness acceptability curve (unadjusted)

Adjusted analysis

Multiple imputation total mean costs were adjusted for baseline variables that were significant predictors of cost. These were: medication count at baseline, EQ-5D-3L at baseline, offset time (time spent in the trial), age, number of hospitalisations for exacerbations in the 12 months prior to randomisation, and number of exacerbations in the 12 months prior to randomisation. A cluster command was used for centre number.

Multiple imputation total mean QALYS were adjusted for baseline variables that were significant predictors of QALYs. These were: baseline EQ-5D-3L, medication count at baseline, offset time, age, gender, hospitalisation for exacerbations in the 12 months prior to randomisation and exacerbations in the 12 months prior to randomisation. A cluster command was used for centre number. These results are presented in *table 31*.

Table 31: Multiple imputation results (adjusted)

	Theophylline Mean (SE)	**Placebo Mean (SE)**	**Difference**	**Cost-effectiveness**
Total costs	£2,784 (£125)	£3,006 (£167)	-£222 (-£472 to £27)	Theophylline dominates, less costs and higher QALYs
Total QALYs	0.621 (0.006)	0.616 (0.007)	0.005 (-0.015 to 0.025)	

When multiple imputation total costs are adjusted, there is a trend towards higher costs in the placebo arm, however this difference is not significant.

Adjusting QALYs for baseline characteristics results in theophylline having higher QALYs than placebo, however, this difference is not significant.

Figure 9 illustrates that when the results are adjusted for baseline characteristics, the results are more uncertain: the majority of total mean costs in the theophylline arm are still less than the placebo arm, although this is now not a significant result. In addition, the QALYs are marginally higher in the theophylline arm, again not a significant result. The ellipse represents the 95% confidence levels.

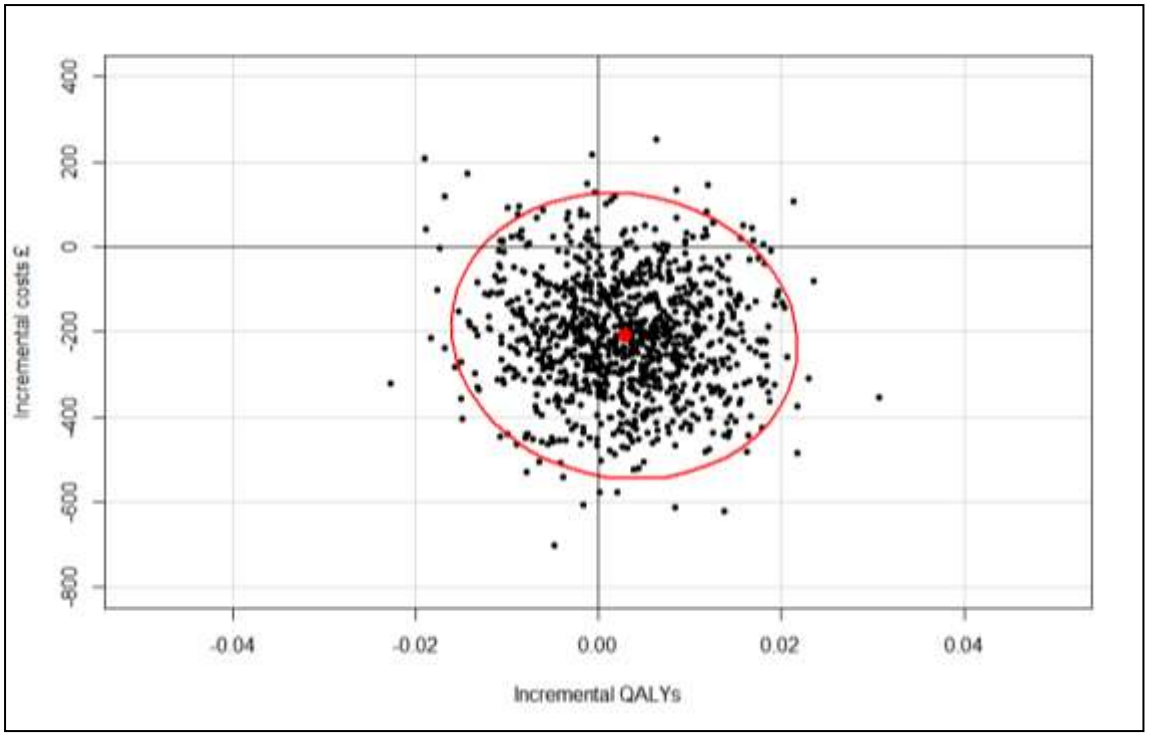


Figure 9: Cost-effectiveness plane (adjusted)

The adjusted bootstrapped results are presented in a cost-effectiveness acceptability curve in *figure 10*. At a willingness to pay of £20,000 there is a 90% chance of theophylline being cost-effective, and at £30,000 there is an 85% chance of theophylline being cost-effective. Again, these results should be viewed with caution as there was no significant difference between arms for QALYs or treatment effect.

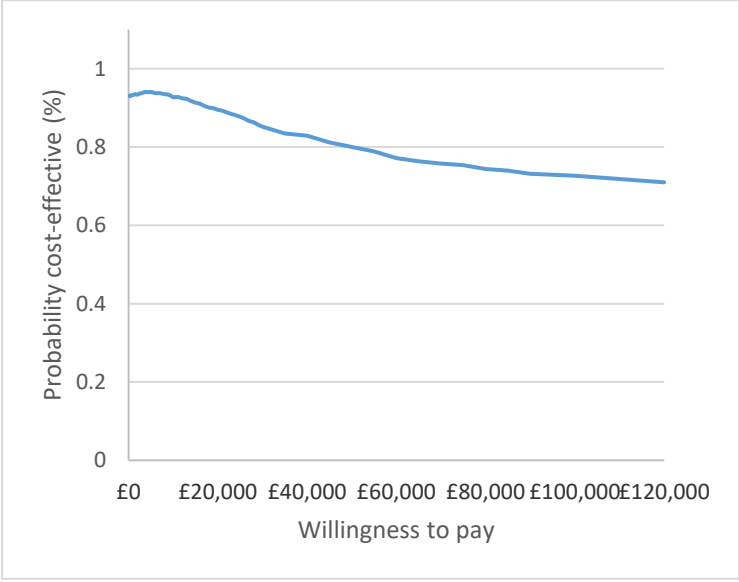


Figure 10: Cost-effectiveness acceptability curve (adjusted)

Exacerbation costs were also adjusted separately to explore the adjustment on the significant difference in exacerbation costs between arms. Strong predictors of exacerbation costs were offset time, hospitalisation for exacerbations in the 12 months prior to randomisation and exacerbations in the 12 months prior to randomisation. A cluster command was used for centre number. These results are presented below in *table 32* and show that for adjusted exacerbation costs, whilst there is a trend for higher costs in the placebo arm, this difference is not significant. The mean costs difference has decreased from £447 to £67.

Table 32: Complete case adjusted exacerbation costs

	Theophylline mean (SE)	**Placebo mean (SE)**	**Difference**	**95% CI**
Total exacerbation cost	£732 (£96)	£799 (£71)	-£67	-£196 to £61
Location costs	£675 (£98)	£735 (£72)	-£60	-£190 to £68
Treatment costs	£58 (£11)	£64 (£8)	-£6	-£19 to £7

CI confidence interval, SE standard error

Cost-effectiveness

For cost per QALY, unadjusted results suggest that whilst theophylline is cheaper than placebo (significant result), the QALYs gained in the placebo arm are higher than in the theophylline arm (non-significant result). The adjusted results suggest that theophylline dominates, it is cheaper with higher QALYs than placebo. However this result should be interpreted with caution; the difference in QALYs is not significant. This is mirrored by the trial primary outcome; theophylline is not clinically effective in terms of reducing exacerbations.

CHAPTER 6 - DISCUSSION

Main results

The results of this trial show that, for people with COPD at high risk of exacerbation, the addition of low-dose oral theophylline to a drug regimen that includes an inhaled corticosteroid, confers no overall clinical or health economic benefit. This result was evident from both the intention to treat and the per-protocol analyses. The primary outcome measure for this trial was the total number of exacerbations of COPD requiring changes in management (minimum management change - use of oral corticosteroids and/or antibiotics) during the one year treatment period, as reported by the participant. For the 11 pre-specified secondary outcome measures, the addition of low-dose theophylline had no clinical or health economic benefit in 10. The addition of low-dose theophylline did reduce the number of COPD exacerbations requiring hospital admission (often classified as 'severe')[68] (adjusted incidence rate ratio 0.72 (95% CI 0.55,0.94)), however further inspection of the data indicated that this difference was the consequence of a small excess of participants allocated to placebo (n=10) having ≥3 hospital treated exacerbations who accounted for 39 of the extra 51 hospital treated exacerbations in the placebo arm. This effect on hospital admissions was also evident on the per-protocol analysis. Given that adjustments for multiple comparisons were not performed, it is possible that this finding could be due to type I error. However, in light of a recent report that another phosphodiesterase inhibitor (roflumilast) is most beneficial in people with prior COPD hospitalization for exacerbation and greater exacerbation frequency,[96] this finding warrants further investigation. The safety data demonstrated that the addition of low-dose theophylline was not associated with an increase in serious adverse events or adverse reactions.

Relevance to existing literature

Oral theophylline has been used in the treatment of COPD and asthma for over 70 years. Conventionally oral theophylline has been used as a bronchodilator in COPD, this effect being mediated by inhibition of phosphodiesterase (PDE), however in order to achieve modest clinical effects relatively high blood concentrations (10-20mg/l) are required but at these concentrations non-specific inhibition of PDE is also associated with a wide range of well recognised side effects, e.g. nausea, palpitations, headaches. A Cochrane Review published in 2010 identified 20 randomised placebo controlled trials of theophylline in COPD, all of crossover design, using dosing schedules to obtain conventional plasma

theophylline levels in the therapeutic range (10-20 mg/l) i.e. conventional high-dose theophylline.[83] The number of participants in these trials ranged from 8 to 60, the total number of participants in the 20 trials was 488. The duration of the studies was 9-90 days, the mean age of participants ranged from 58 to 69 years, four of the studies were graded as high quality. The systematic review demonstrated that use of high-dose conventional theophylline resulted in a small but significant increase in FEV_1 of 100ml (95% CI; 40, 160), this was derived from 13 studies with 244 participants. Two studies with a total of 45 participants reported on the incidence of exacerbations, concluding that high-dose conventional theophylline had no effect on the incidence of exacerbations. Three studies with a total of 64 participants reported data on nausea, with the risk of experiencing nausea when on theophylline treatment being significantly increased (RR 7.67; 95%CI 1.47, 39.94). When compared with previous trials of conventional high-dose theophylline in COPD the current trial of low-dose theophylline that recruited 1578 participants is clearly somewhat larger and the treatment period longer in duration. Moreover in contrast to conventional high-dose theophylline trials with their focus on lung function, the primary outcome of the current study was exacerbations of COPD and the study population comprised participants at high risk of exacerbating. When compared with these trials of high-dose conventional theophylline the current trial, as expected, showed no effect of low-dose theophylline on lung function (FEV_1) and reassuringly no increase in side effects. One of the findings from the Cochrane Review was that very few participants withdrew from intervention trials of high-dose conventional theophylline for any reason. In the Review, nine studies reported no 'dropouts' and in the remaining studies the dropout out rate was generally very low, the only exception to this low 'dropout' rate was the study of Guyatt who reported eight withdrawals from 27 recruited (30%).[97] The sample size of the current trial included an estimate of 6% of participants ceasing taking their study medication based on the four high quality studies reported in the Cochrane Review,[83] in which three of 51 (6%) participants 'dropped out'. The 26% of participants ceasing study medication in the current study is greater than anticipated (although balanced across the arms) and more in keeping with the study of Guyatt,[97] probably reflecting the pragmatic nature of the current trial, the older age of participants and the much longer duration of the current trial when compared with those in the Cochrane Review.

The use of high-dose conventional theophylline has declined over the years because of its narrow therapeutic index, modest clinical effect, side effect profile, drug interactions, the need for blood concentration monitoring and the availability of more effective inhaled

therapies.[98] High-dose conventional theophylline is now included in current COPD guidelines as a third line therapy.[1]

The concept of using low-dose theophylline to augment the anti-inflammatory effects of corticosteroids on the airway inflammatory processes in COPD originated from *in vitro* and animal studies investigating the molecular mechanisms contributing to the reduced corticosteroid sensitivity of COPD.[32, 38-40, 43, 46] The key observation was that the reduced HDAC2 activity of COPD can be reversed by low concentrations (1-5mg/l) of theophylline, moreover theophylline reduces corticosteroid insensitivity in COPD such that there is a marked synergistic interaction between theophylline and corticosteroids in suppressing the release of inflammatory mediators from alveolar macrophages obtained from COPD patients.[43, 44] These basic research studies suggest that low-dose (1-5mg/l) theophylline could increase HDAC activity and hence reduce corticosteroid resistance in COPD patients thereby enabling ICS to switch off inflammation and potentially more effectively reduce exacerbation rates.

Prior to commencing the current study, the concept of using low-dose theophylline in conjunction with corticosteroids in COPD had been explored in two small RCTs. The first RCT was in 35 patients admitted to a Spanish hospital with an acute exacerbation of COPD who were treated with a regime that included systemic corticosteroids.[48] Participants were randomised to receive additional low-dose theophylline or nothing in a single blind design, participants not on ICS at admission were commenced on ICS. After three months of treatment low-dose theophylline increased sputum macrophage HDAC activity and reduced sputum concentrations of the pro-inflammatory mediators IL-8 and TNF-α. There were no clinically significant effects in this small study, although fewer participants in the theophylline group had a subsequent exacerbation than in the control group (12.5% vs 26%). This study differed from the current study: small sample size, single blinded, no placebo control, three month follow up, participants were only recruited during hospitalisation with exacerbations of COPD, all were male, and only 14% had had ≥2 exacerbations in the previous year. Notably 26% of participants were not followed up at three months.

The second small (n=30) RCT of COPD patients was of double dummy (low-dose theophylline vs placebo, standardised dose of ICS vs placebo), randomised double blind, parallel study based in the UK.[49] After four weeks of low-dose theophylline there was no

effect on the primary outcome of absolute number of sputum neutrophils. The combination of low-dose theophylline/ICS significantly reduced a number of secondary endpoints (e.g. sputum percentage neutrophils, sputum total eosinophil count). In an open label extension of the trial the combination of low-dose theophylline/ICS increased peripheral blood mononuclear cell HDAC activity by nine-fold. The study concluded that the combination of ICS and low-dose theophylline may attenuate airway inflammation in patients with COPD. One of the limitations of this study was that the significant findings were for low-dose theophylline/ICS vs theophylline rather than low-dose theophylline/ICS vs ICS suggesting perhaps that the observed effects were a consequence of the ICS and not the low-dose theophylline. This study differs from the current study: four week duration, small numbers, 83% male, younger age (61 years) although lung function (mean FEV_1 54%) was similar.

Whilst the current trial was being conducted two trials investigating the therapeutic consequences of low-dose theophylline were published.[52, 99] The first study from India was a hospital based single blinded, prospective, randomized, placebo controlled study that investigated the effects of adding low-dose theophylline to the combination of formoterol plus budesonide.[99] A total of 58 patients with moderate/severe COPD were commenced on a standardised ICS/LABA therapy (budesonide and formoterol) and were randomised to receive either low-dose theophylline or placebo for 60 days. Fifty participants completed the trial and their data presented. The addition of low-dose theophylline resulted in a greater improvement in total symptom scores, a greater increase in FEV_1 and a greater increase in 6 minute walking distance when compared with placebo. Of note, however, the method of randomisation was not described, the actual number of participants randomised to each treatment group was not presented, the nature of the 'single blind' was not explained and there was no 'intention to treat' analysis. The randomisation appeared not to have eliminated potential sources of bias, the participants allocated to low-dose theophylline were clearly more severely affected by COPD: their respiratory rate was greater (20.7 vs 18.7, p=0.003); their FEV_1 was lower (49% vs 57% predicted, p=0.05); their symptom scores were greater (10.17 vs 8.37, p=0.003); their 6 minute walking distance shorter (373 vs 409m, p=0.07); and more were classified as severe (54% vs 27%, p=0.09), moreover the placebo tablets were described as similar rather than identical. These differences could reflect a bias for the more severely affected participants to be preferentially allocated to the low-dose theophylline arm of the trial. This study differs from the current study: sample size was much smaller, hospital based; 92% of participants were male; younger age ~55 years; BMI was lower ~17 kg/m^2; 60

day treatment period and single blinded. In addition to the issues regarding blinding and randomisation the results of the trial also raise the possibility that whilst the intention was to investigate low-dose theophylline, in reality conventional high-dose theophylline was being tested: an improvement in FEV_1 was described with theophylline treatment, the dosing regimen for this study was 400mg theophylline for a weight >50kg, 300mg for a weight of 40-50kg and 200mg for <40kg, however a significant proportion of participants appeared to be underweight with a mean BMI of ~17 kg/m^2, and theophylline treatment resulted in higher incidences of typical high-dose theophylline toxicity symptoms such as nausea, vomiting, headache, palpitation and insomnia. In the current study this was avoided by basing theophylline dose on ideal body weight and smoking status.

The second study, the Spanish Low-dose Theophylline as Anti-inflammatory Enhancer in Severe Chronic Obstructive Pulmonary Disease (ASSET) trial was a multicentre, randomised, double-blind, placebo-controlled trial that recruited patients with COPD whilst hospitalised for a COPD exacerbation.[52] Participants were randomised to low-dose theophylline (100mg twice a day) or matched placebo in addition to ICS/LABA treatment, participants not routine taking ICS/LABA were established on ICS/LABA. In total 70 patients were randomised (36 theophylline, 34 placebo) and 46 completed the year of treatment (23 theophylline, 23 placebo). The co-primary outcomes were change in HDAC and exacerbation frequency during the one year treatment period. The addition of low-dose theophylline had no effect on plasma/sputum HDAC concentrations and no effect on COPD exacerbation rate (theophylline vs placebo, 0.97 (SD 0.94) vs 0.88 (SD 0.89)). This trial has some similarities with the current trial: primary outcome of exacerbation; same definition of exacerbation; one year treatment period; similar participant age CAT score and levels of cardiovascular comorbidity at baseline; no significant difference in adverse reactions between groups. However, there are some important differences between this trial (ASSET) and the current study (TWICS). The current study is much larger (n=1578) than ASSET (n=70), being designed to detect a 15% reduction in exacerbations with 90% power, whereas ASSET was designed to detect an arguably implausibly large 50% reduction in exacerbations with 80% power. The exacerbation rate in ASSET was about half that observed for TWICS (0.92 vs 2.23/yr). Perhaps the most plausible explanation for this is that all participants in the ASSET trial were recruited whilst hospitalised with an exacerbation of COPD irrespective of exacerbation history, whereas participants in TWICS were clinically stable, 60% were identified from primary care and all had a history of ≥2 exacerbations in the previous year

requiring treatment with antibiotics and/or corticosteroids. The proportion of participants ceasing study medication was possibly higher in ASSET than in TWICS (34% vs 26%), however it should be noted that 14% of participants in ASSET ceased study medication because their FEV_1 improved to >50% predicted during the one year treatment period. This is most likely to be a consequence of ASSET recruiting in the peri-exacerbation period and TWICS recruiting when participants were clinically stable. When compared with TWICS, participants in ASSET were more likely to be male, had more severe COPD (lower FEV_1), more likely to be hospitalised during the treatment period but less likely to be diabetic (probably reflecting the higher mean BMI of TWICS participants, 27 vs 22 kg/m^2).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) management strategy guideline highlights that the clinical relevance of low-dose theophylline has not been fully established and that clinical evidence on low-dose theophylline, particularly on exacerbations, is limited and contradictory.[1] TWICS is the first large pragmatic community based trial to investigate the effect of adding low-dose theophylline to the treatment regimen of people with COPD who are at high risk of exacerbating despite a treatment regime that includes maintenance inhaled corticosteroids in COPD.

Pre-clinical work convincingly demonstrates that the combination of low-dose theophylline and corticosteroid has a strong biological effect, increasing HDAC and inhibiting the release of pro-inflammatory mediators.[38, 39, 41-44] The trials conducted to date have been small (n=30-70), hospital based, and have tended to focus on biological outcomes with short treatment periods.[48, 49, 52, 99] The largest trial to date in this field has reported that low-dose theophylline had no effect on HDAC or exacerbations, however as the authors of ASSET acknowledge, *'we might have overestimated the potential clinical benefit when we calculated the sample size, which may have precluded us from identifying a clear-cut clinical effect.'.*[52] The TWICS trial avoids many of the limitations of previous studies and clearly demonstrates that in an NHS setting that for people with COPD, the addition of low-dose oral theophylline to a drug regimen that includes an inhaled corticosteroid, confers no overall clinical benefit. The participants in TWICS were a group of people with COPD at high risk of exacerbating based on their history of exacerbating in the previous year, this group was deliberately chosen because of their impact on the NHS and it enabled us to design a trial of realistic (but ambitious) sample size. Although TWICS did not investigate whether people with COPD at low risk of exacerbation would benefit from low-dose theophylline, the combination of the

findings of TWICS and the absence of a biological effect (HDAC concentrations) in the ASSET trial despite a sample size *'more than enough to demonstrate a biological effect of the intervention'*[52] make it highly unlikely that low-dose theophylline would be beneficial in low exacerbation risk COPD patients. A possible explanation for the disparity between the biological effects observed in previous studies, with short treatment periods, and the absence of beneficial effects in TWICS, with a year long treatment period, is that any biologically beneficial effect of low-dose theophylline is not sustained in the long term.

Cost-effectiveness

The health economics results indicate that after adjustment for baseline characteristics there was no significant difference in the total health economic costs associated with treatment with low-dose theophylline compared with placebo: adjusted mean difference -£222 (95% CI -£27 to £472). With unadjusted complete case data the total costs are higher in the placebo arm compared to the theophylline arm, a significant difference of £452 (95% CI £132 to £771). This difference was driven by a greater number of participants in the placebo arm receiving treatment for exacerbations in hospital, compared the theophylline arm. The ten most costly observations (over £10,000) were all in the placebo arm, and were the result of hospital stays of greater than 40 days. The multiple imputation results mirror the complete case results with a significant difference in unadjusted costs of £439 (95% CI £32 to £846), higher in the placebo arm.

The difference between arms in total costs is driven solely by the hospital treated exacerbations and exacerbations treated with oxygen, no other resource group has a significant difference between arms. The difference in the number of exacerbations receiving hospital treatment is likely to be the result of a small number of participants in the placebo arm having very frequent hospital admissions. Therefore these results should be interpreted with caution.

Exacerbation costs are 22%-33% of the total costs (theophylline and placebo respectively) which is somewhat less than the 60% reported by Britton et al[27] in 2003 perhaps reflecting differences in management between 2003 and 2015/6 particularly increased use of preventative drugs, pulmonary rehabilitation and more structured chronic disease management in primary care.

The economic outcome of QALYs was higher in the placebo arm in the unadjusted complete case results than in the theophylline arm, however this difference is not significant 0.011 (95% CI -0.018 to 0.040). Multiple imputation results mirrored the complete case results; there were no significant differences, with unadjusted results favouring the placebo arm, and adjusted results favouring the theophylline arm.

These results reflect the primary outcome of number of exacerbations needing treatment in the 12 month follow-up period; there was no significant difference between arms.

Hettle et al[100] reported 4 year UK costs in their paper on tiotropium versus usual care in the UK and Belgium. Exacerbation costs ranged from £2,295 to £2,744, (£574 to £686 per year) and maintenance costs ranged from £2,935 to £3,937 (£737 to £984 per year). This compares to one year costs from this research of; exacerbations £585 to £1,033, and maintenance costs of £2,074 to £2,101. Whilst the annual exacerbation costs of the current study are similar to that of Hettle et al, the maintenance costs are somewhat higher reflecting the older age of the participants of the current study (68.4 years vs 64 years), that 80% of the current participants were prescribed LAMAs (none for usual care in Hettle study), people with COPD using long term oxygen were included in the current study and in the current study participants were more likely to be in the severest GOLD category (14% vs 8%). Hettle et al also reported a 33 times higher cost for hospitalised exacerbations compared to non-hospitalised exacerbations in Belgium, reflecting the increased cost between hospitalised and non-hospitalised exacerbations in this research.

The strengths of this research include; few participants with no outcome or resource use (low number of missing cases; 4.3%); uncertainty was explored using non-parametric bootstrapping; and where there was a significant difference in exacerbation costs this was explored further to identify what was driving this difference.

The two main limitations to the cost-effectiveness analysis include; the number of missing EQ-5D-3L questionnaires (19.1%) and that small amounts of missing data were imputed using naïve methods at disaggregated level.

Strengths and limitations

The main strength of TWICS is that it was a large pragmatic, predominantly community based, suitably powered, double blind randomised, placebo-controlled, UK multicentre clinical trial with a high follow-up rate for the primary clinical outcome. A total of 1578 individuals were recruited in 121 UK sites, 60% of participants were identified in primary care making it highly likely that TWICS participants reflected normal clinical practice across both primary and secondary care in the UK. The one year treatment period allowed capture of the seasonality of exacerbations.[101]

Originally TWICS aimed to recruit 1424 participants, the sample size being primarily based on the findings of the observational ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohort study of 2138 COPD patients recruited in 46 centres from 12 countries.[21] ECLIPSE demonstrated that the best predictor of an exacerbation in a year, was a treated exacerbation in the previous year. In addition, ECLIPSE identified a frequent exacerbator phenotype defined as ≥2 exacerbations in the previous year, moreover this frequent exacerbator phenotype was relatively stable for three years and could be reliably identified by patient report. For the frequent exacerbating patients recruited into TWICS, data from ECLIPSE predicted a mean 2.22 (SD 1.86) exacerbations in the year of treatment and the sample size for TWICS was based on this. This prediction proved to be remarkably close to what we observed, increasing confidence in the findings, with a mean number of exacerbations in the theophylline arm of 2.24 (SD 1.99) and in the placebo arm 2.23 (SD 1.97). A notable finding of TWICS was an apparent disparity between the number of exacerbations reported by participants in the year prior to the study (mean 3.59, SD 2.15) whereas in the treatment year the number of self-reported exacerbations was somewhat less (mean 2.23, SD 1.99). The most likely explanation for this disparity is that we did not ask for dates for the reported exacerbations in the year prior to the study, whereas during the study we asked for dates and the conventional minimum of two weeks between consecutive exacerbation episodes was necessary to consider exacerbations as separate,[68] this resulted in exacerbations separated by less than two weeks being merged. Although further factors contributing to the disparity in exacerbations before, and during the study may include an over-reporting bias by participants and regression to the mean, the exacerbation frequency during the treatment period was remarkably consistent with that predicted by ECLIPSE. Although the exacerbation rate observed in the current trial is somewhat higher than recent explanatory trials[102, 103], it is entirely consistent with the recent pragmatic UK Salford Lung

Study.[104] The Salford Lung Study with an inclusion criterion of ≥1 exacerbation in the previous year reported exacerbation rates of 1.74-1.90/year, the slightly higher exacerbation rate in the current trial most likely reflects the participants' increased propensity to exacerbate (≥2 exacerbations in the previous year) as well as the lack of requirement to withhold therapy other than theophylline meaning investigators were happier to recruit higher risk patients. . Although the diagnosis of COPD was confirmed by post-bronchodilator FEV1/FVC <0.7, 18.3% of participants reported a concurrent/previous diagnosis of asthma. Whilst this may, in part reflect a diagnostic bias towards the more socially acceptable diagnosis of asthma in the past, it is possible that the current trial included up to 18% of participants with asthma COPD overlap syndrome. Whilst it may be possible that these patients may respond differently to the theophylline this was not one of the study objectives.

By recruiting 1578 individuals, 60% of whom were identified in primary care, TWICS exceeded its original recruitment target of 1424 with at least 50% being recruited in primary care. It was initially envisaged that TWICS would recruit from a limited number (seven) secondary care sites with primary care sites acting as PIC sites for these secondary care centres. Recruitment to TWICS was delayed by five months because of a worldwide shortage of bottle tops for the drug bottles. Initially recruitment in 16 primary and six secondary care sites was on target and TWICS achieved its recruitment targets for the feasibility phase by recruiting 100 participants in months 7, 8 & 9 with 55% identified in primary care. Within four months it became apparent that it would not be possible to sustain recruitment with recruitment falling below the required 59/month to a nadir of 26 in month 15 (October 2014). To address this, a change in recruitment strategy was implemented in month 12 (July 2014) with rapid increases in the number and rate of opening up primary and secondary care sites. Ultimately 121 recruiting sites were opened up comprising: 88 primary care sites and 33 secondary care sites. Other primary care practices acted as PICs for primary and secondary care sites. In total 477 participants were recruited and followed up entirely in primary care, 464 participants were identified in primary care but recruited and followed up in secondary care (this was particularly the case in Scotland) and 637 participants were identified, recruited and followed up in secondary care. This change in recruitment strategy was successful with monthly recruitment remaining above 50/month from month 19 and reaching a peak of 81 in month 35.

Primary outcome data (number of COPD exacerbations) were collected on 98% of the 1567 participants who commenced the one year treatment period (1578 recruited less 11 post-randomisation exclusions). Several factors contributed to the high follow-up rate. TWICS was designed to be as inclusive as possible by facilitating participation by people with COPD who would normally find it too difficult to participate in a trial because of their ill health. The trial was designed to be relatively 'light touch' with three study visits to a local study centre, if participants were unable to attend for assessment, they were visited at home, contacted by telephone, or sent the questionnaires to complete at home. Participation and remote follow-up was further facilitated by delivering the study drug to the participants' homes using a third party distributor. All participants who ceased taking the study drug were invited to remain in the study for follow-up, either by face to face assessment, telephone assessment or postal questionnaire. For participants who could not be followed-up directly e.g. failed to attend follow-up, various methods of follow-up, independent of participant involvement were used. In the first instance the participant's GP was sent a questionnaire enquiring about exacerbations (number, dates, how and where treated), the minimum data requested were the number of exacerbations in the treatment period. Failing this, GP surgeries were contacted by telephone or a request was made for a redacted copy of patient encounter summaries from which the Co-CI extracted exacerbation data. The combination of follow-up methods enabled the intention to treat analysis to include 1489 years of participant follow-up data. Inevitably there were some participants who did not provide a full 12 months of follow-up data e.g. deaths, or for whom 12 months of follow-up data were not available even using remote follow-up method. A strength of TWICS was that the statistical analytical methods used enabled inclusion of these participants up to the point at which they were lost to follow-up with their time in study utilised in the offset variable during analysis.

Previous studies investigating the potential anti-inflammatory effects of low-dose theophylline in COPD and asthma (not in conjunction with ICS) have used a 'one size fits all' dosing approach e.g. all participants received 100 mg bd or 200 mg bd.[43, 44, 48, 99, 105-107] In contrast, one of the strengths of TWICS was that theophylline dosing was somewhat personalised, being determined by ideal body weight (IBW) and smoking status. As noted in our protocol paper,[55] population studies have demonstrated that theophylline pharmacokinetics are influenced by weight, COPD disease status (reduced clearance) and smoking (increased clearance).[57-66, 108] Smoking induces theophylline clearance by approximately 60% that gradually returns to normal levels upon smoking cessation. This was

incorporated into the definition of a non-smoker in TWICS and procedures were implemented to modify, where necessary, the dose of study drug in a timely manner if participants changed their smoking status during the treatment period. The use of IBW in preference to actual weight avoided the potential for giving an inappropriately high dose of theophylline to obese participants. In TWICS theophylline dosing was based upon pharmacokinetic modelling incorporating the major determinants of theophylline steady state concentration, i.e. weight, smoking status, clearance of theophylline (low, normal, high), and was designed to achieve a steady state plasma theophylline concentration of 1-5 mg/l and certainly to be <10 mg/l[55]. Theophylline is metabolised in the liver by the enzyme CYP1A2 which is induced by smoking and inhibited by a number of medications with a consequent increase in plasma theophylline concentration. For this reason, the exclusion criteria included long-term use of drugs with the potential to increase plasma theophylline concentration,[94] conversely concomitant use of drugs with the potential to lower plasma theophylline concentration were permitted in the trial. Reassuringly the dosing regimen used for TWICS appeared to be effective in establishing low-dose plasma theophylline concentrations of 1-5mg/l because there was no evidence of the typical sequelae of conventional high-dose theophylline such as an improvement in FEV_1. In addition, when compared with the placebo group, there was no evidence that participants allocated to low-dose theophylline experienced more serious adverse events or adverse reactions, nor did the low-dose theophylline report more serious adverse events or adverse reactions typical of theophylline toxicity, namely gastro-intestinal, cardiac, psychological or neurological symptoms. Furthermore when the reasons for ceasing study medication were analysed there were no significant differences between the arms, notably for gastro-intestinal, cardiac, psychological or neurological symptoms typical of theophylline toxicity. A consequence of the personalised dosing of study drug to achieve a low-dose plasma theophylline concentration well below that associated with typical side effects was that there was no need for blood sampling to monitor plasma theophylline, a necessity that would have greatly increased the complexity of the trial and increased the likelihood of unblinding the participant and/or investigator. The absence of blood testing reduced costs and was extremely popular with primary care sites and contributed to the willingness of many primary care sites to participate in TWICS. The potential limitation of relying on participant reported smoking status is perhaps less important in this study, as a smoker declaring themselves to be a non-smoker would have resulted in the lower dose of theophylline being prescribed, perhaps ensuring plasma theophylline to be in the low-dose range of 1-5mg/l.

As with all studies, there are limitations associated with TWICS. The primary outcome for the study was the number of participant reported exacerbations during the one year treatment period, to facilitate recall participants were given a diary card to make notes on exacerbations, treatment, and healthcare usage. The definition of an exacerbation was the widely used ATS/ERS guideline recommendation of a worsening of patient's dyspnoea, cough or sputum beyond day-to-day variability sufficient to warrant a change in management.[68] The minimum management change was treatment with antibiotics or oral corticosteroids, and consequently, the TWICS study only quantified moderate and severe exacerbations. However, these exacerbations are the ones which are the most burdensome to patients and health care services. A limitation of TWICS is that the relatively conservative definition of exacerbation probably underestimates the frequency of symptom-defined mild exacerbations that are short lived and treated by the patient with a temporary increase in bronchodilator therapy,[109] the identification of such mild exacerbations would have required participants to complete daily symptom diary cards adding to the intrusiveness of the study and considerably adding to the data entry burden of research staff. Although TWICS did not quantify mild exacerbations there were no significant differences between treatment and placebo in quality of life/impact on health status as quantified by EQ-5D-3L/CAT suggesting either that low-dose theophylline had no effect on mild exacerbations or if there was an effect it did not impact on health status/healthcare usage.

A possible limitation of participant reported exacerbations is the accuracy of such a report over a six month period. Whilst it would have been possible to obtain such exacerbation data from healthcare records it is well documented that people with COPD do not report all of their exacerbations to healthcare professionals.[18, 110-112] Patient recall of COPD exacerbations has been shown to be highly reliable over a year: in the London COPD Cohort study there was no significant difference between the number of exacerbations recorded on diary cards and patient estimates of their exacerbation number over the same one year period (mean 2.4, SD 2.2 vs mean 2.3 SD 2.1), there was 93% agreement between patient recalled and diary-recorded exacerbations.[112] There was however, a difference between the number of treated exacerbations recorded on diary cards and the number of treated exacerbations remembered by the patient over the same one year period (mean 2.3 SD 2.1 vs 1.8 SD 1.8), there was 88.6% agreement between patient recalled and diary-recorded treated exacerbations.[112] The patient representatives helping with TWICS were adamant that it was fairly straight forward

to recall the number of exacerbations over a six month period. A small validation exercise was conducted at two of the largest sites (Aberdeen and Aintree) during TWICS to confirm that participant recall was indeed valid. The validation was done by requesting a care/encounter summary from the GP and comparing this against participant report. In Aberdeen, 43 records (20% sample) were checked; and in 37 there was complete agreement between participant and GP report. In Aintree, 24 records were been checked and in 16 there was complete agreement between patient and GP report. Therefore in a 4% sample of participants there was 80% agreement. This rate of agreement was slightly lower than that reported by Quint et al[112] however, current GP records may not be as reliable a source of exacerbation data as in the past, given that patients have rescue packs at home and can access help for their exacerbations through many non-GP sources, e.g. pharmacies, emergency and walk-in centres, Accident and Emergency departments etc.

A limitation of TWICS was that more participants ceased taking their study drugs (26%) than anticipated (6%), although this was somewhat offset by 10% over-recruitment (n=154). There was no evidence of bias in ceasing study medication with the proportion and the reasons given for ceasing study medication being equally distributed between those allocated to low-dose theophylline and those allocated to placebo. The original sample size for TWICS (n=1424) accounted for 6% of participants ceasing taking their study medication based on the four high quality studies reported in a Cochrane Review of theophylline in COPD, in which three of 51 (6%) participants 'dropped out'.[83] In reality 413 of the 1578 participants either never started/initiated medication (post randomisation exclusions n=11, non-initiation n=8) or ceased taking the study medication (non-persistence, n=393), this 26% rate of ceasing study medication is greater than anticipated but in keeping with ASSET trial of low-dose theophylline that reported a 34% rate for ceasing study medication.[44] The higher than anticipated rate of ceasing study medication in TWICS was most likely the consequence of the relatively high rates of co-morbidities in participants giving rise to symptoms that were attributed to the study medication and a heightened awareness of adverse reactions listed in the PIL and the package insert accompanying the study medication. This is consistent with 46% of participants reporting adverse reactions typical of high-dose theophylline (but equally distributed between the two study arms) and why 20% of those ceasing study medication gave gastrointestinal symptoms as the reason for ceasing study medication although there was no significant difference in the incidence of such symptoms in those ceasing low-dose theophylline and those ceasing placebo. Some participants were asked to discontinue study

medication because they had stopped taking an ICS. During the trial there was an emergent change in prescribing practice away from ICS containing preparations to LABA/LAMA inhalers, however this had minimal impact on the trial (certainly <20 participants), most probably because the participants in this study were at high risk of exacerbation and for whom there is still a role for ICS. Although 413 participants ceased study medication during TWICS, a review of the medication returns indicated that 66 of these participants had >70% adherence whilst taking the study medication when averaged over the 12 month treatment period, e.g ceased study medication at 11 months; these individuals were included in the per-protocol analysis. Although per protocol analyses, are biased by their very nature the per-protocol analysis for this study included 1142 years of participant data (85% of the 1338 years indicated by the power calculation) it is not surprising that the results of the per-protocol analysis were almost identical to that of the intention to treat analysis. Although adherence with the study medication was quantified through pill counting it was not practical to assess adherence to the inhaled corticosteroid as this would have entailed use of non-routine care methodologies such as diaries cards, metered inhalers etc. The rationale for the use of low-dose theophylline is as an adjunct to ICS therapy, that we were unable to verify adherence to ICS therapy is a limitation of this study.

Generalisability

This study has good external validity as it was of a pragmatic design that reflected normal clinical practice across both primary and secondary care in the UK. Participants remained on their existing COPD medications, they were managed in the normal way by their usual healthcare teams and the trial recruited from 121 sites (88 primary care, 33 secondary care) that spanned the UK, many of the secondary care sites were District General Hospitals. We consider it to be highly likely that TWICS participants are typical of normal clinical practice across both primary and secondary care in the UK and that the findings are generalizable to clinical practice in the UK.

The TWICS study recruited participants highly likely to exacerbate in the one year treatment period as evidenced by two or more treated exacerbations in the previous year. In contrast to many COPD trials we did not exclude potential participants with mild COPD, as evidenced by FEV_1>80% predicted, 9% of TWICS participants had mild COPD based on spirometry criteria but fulfilled the frequent exacerbator phenotype,[21] enhancing the generalisability of the trial. Recruitment to TWICS was limited to frequent exacerbators because in clinic

practice these are the patients who are usually commenced on this 'third line' therapy,[24] moreover a trial of participants less likely to exacerbate e.g. one exacerbation in previous year, would have been much larger (n ~3000) and somewhat more costly. Although we did not test whether the addition of low-dose theophylline to ICS had an effect on people who were less frequent exacerbators there is no scientific or clinical reason why low-dose theophylline should have a differential effect on frequent/infrequent exacerbators and it would seem reasonable to extend the findings of the current study to people with COPD at low risk of exacerbating.

Whilst the results of this trial are generalizable to the UK and probably other high income countries, the findings may not be applicable to low/medium income countries, with differing pharmacogenetic profiles, where theophylline remains a frequently used therapy in COPD most probably because it is inexpensive compared to inhaled therapies.[113-116] The randomised double blind placebo controlled trial of Zhou et al raises the possibility that in China at least, there is a therapeutic response to low-dose theophylline in the absence of ICS.[117] In this trial the addition of low-dose theophylline to usual COPD treatment in 110 people with COPD (theophylline n=57, placebo n=53) for a year significantly reduced the frequency of exacerbations when compared with the placebo group (0.79 SD 1.16 vs 1.70 SD 2.61, p=0.047). The participants in this trial differed considerably from those taking part in TWICS: only 30% were taking regular medication prior to the trial and this was restricted to inhaled salbutamol; use of ICS, LABA and LAMA were excluded; the target plasma theophylline concentration (5-10mg/l) was also somewhat higher than the target range (1-5mg/l) identified for optimum synergistic interaction between corticosteroids and low-dose theophylline. The use of low-dose theophylline in conjunction with corticosteroids in China is being addressed by the ongoing theophylline and steroids in COPD study (TASCS) that is recruiting 2400 people with COPD in China.[118] They are being randomly allocated to low-dose prednisolone (5mg once a day) or low-dose theophylline (100mg twice a day) with low dose prednisolone (5mg once a day) for 48 weeks. The primary outcome is exacerbation rate over the 48 week treatment period. The trial is due to be completed by June 2018. It will be interesting to compare the results of TASCS with TWICS, although it should be noted that the routine use of oral corticosteroids as a maintenance treatment for COPD, even though they are cheaper than ICS, would never be contemplated in developed countries for clinical and ethical reasons.

Public and Patient Involvement

Public and patient involvement in this study was limited but effective, nevertheless lessons were learnt that have been implemented in a subsequent NIHR-HTA funded study, e.g. a person with COPD is a joint grant holder.

A patient with COPD was a voting member of the TWICS TSC, recruitment and retention of a patient representative was hindered by ill health. The first patient approached declined because of ill health. The patient representative nominated by Chest Heart and Stroke Scotland as part of their Voices Scotland initiative had to resign because of ill health and a third patient representative was identified and he has made an active contribution to the TWICS study. Supporting the TSC patient representative was actively undertaken by several members of the local study team. In our subsequent NIHR-HTA funded trial we have a patient representative who is supported by CHSS's Voices Scotland lead who is not only a voting member of the TSC but also co-ordinator and representative of a panel of 15 COPD patients (as they like to be called).

A representative of the British Lung Foundation and a person with COPD made important contributions to study design procedures (what was acceptable - spirometry, and what was not acceptable - daily diary cards), perhaps the most important suggestions were to deliver trial medication to home addresses, and to facilitate follow-up for ill participants by way of home visits, telephone, and postal questionnaires. Public and patient involvement resulted in many changes to the design and content of the 'short' PIL (a one page summary PIL), and the 'long' PIL (a more detailed PIL) and the importance of these changes is evidenced by the in success recruitment and there were no changes to the PIL throughout the study. Public and patient involvement was particularly insightful during TSC deliberations concerning the validity of patient recall of COPD exacerbations.

The support of the BLF and CHSS has been invaluable throughout the study, identifying volunteers for public and patient involvement and publicising the study.

Conclusions

Main conclusions

This is the first adequately powered multi-centre pragmatic double blind randomised placebo controlled trial to assess the effectiveness of adding low-dose theophylline to a drug regimen

containing inhaled corticosteroids in people with COPD at high risk of exacerbation, the analyses demonstrated that low-dose theophylline has no overall clinical or health economic benefit.

Implications for practice

The trial has shown that low-dose theophylline has no overall clinical impact when added to inhaled corticosteroids in COPD. We anticipate that the results of the trial will be incorporated in an ongoing systematic review of theophylline in COPD.[119] Given that TWICS is one of the largest trials of theophylline to date, we anticipate that it will have a major influence on the meta-analyses and conclusions. National and International COPD Guidelines should take the results of TWICS into account when making recommendations on the treatment of COPD and the prevention of exacerbations of COPD. In the meantime clinical commissioners can now be encouraged to make informed decisions regarding the use theophylline in COPD.

Recommendations for research

The findings from one of the planned secondary analyses was that low-dose theophylline reduces the rate of admission to hospital because of severe COPD exacerbation. Whilst it is possible that this may be a chance finding, it is consistent with a recent report that roflumilast is most beneficial in people with prior COPD hospitalization for exacerbation and greater exacerbation frequency. A further study investigating the effect of low-dose theophylline in people with COPD who frequently exacerbate and are admitted to hospital is justifiable given their disproportionate impact on NHS resources.

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Contributions of authors

Graham Devereux (Co-Chief Investigator) contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

Seonaidh Cotton contributed to the design of the trial, was responsible for the day-to-day management of the trial, and contributed to the interpretation of results and writing/editing the report.

Shona Fielding contributed to the design of the trial, was responsible for statistical analysis, and contributed to the interpretation of results and writing/editing the report.

Nicola McMeekin was responsible for the health economic analysis and contributed to the interpretation of results and writing/editing the report.

Peter Barnes contributed to the conception and design of the trial, the interpretation of results and writing/editing the report.

Andy Briggs contributed to the conception and design of the trial, oversaw the health economic analysis and contributed to the interpretation of results and writing/editing the report.

Graham Burns contributed to the conception and design of the trial, the interpretation of results and writing/editing the report.

Rekha Chaudhuri contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

Henry Chrystyn contributed to the conception and design of the trial, the interpretation of results and writing/editing the report.

Lisa Davies contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

Anthony De Soyza contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

Simon Gompertz contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

John Haughney contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.
Karen Innes was responsible for aspects of the day-to-day management of the trial, and contributed to the interpretation of results and writing/editing the report.
Joanna Kaniewska was responsible for aspects of the day-to-day management of the trial, and contributed to the interpretation of results and writing/editing the report.
Amanda Lee contributed to the conception and design of the trial, oversaw the statistical analysis and contributed to the interpretation of results and writing/editing the report.
Alyn Morice contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.
John Norrie contributed to the conception and the design of the trial, the conduct of the trial, the interpretation of results and writing/editing the report.
Anita Sullivan contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.
Andrew Wilson contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.
David Price (Co-Chief Investigator) contributed to the conception and design of the trial, the conduct of the trial, the interpretation of the results and writing/editing the report.

Data sharing statement
All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

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Staff at recruitment sites

Secondary care sites	
Aberdeen Royal Infirmary	Ratna Alluri, Faye Annison, David Christie, Michael Christie, Patricia Cooper, Lisa Davidson, Graham Devereux (PI), Margaret Fernie, Vicki Fraser, Amber Johnson, Alison McKay, Celia Meneses, Joy Miller, Beth Robb, Catriona (Tina) Stewart
Aintree University Hospital NHS Foundation Trust	Lisa Davies (PI), Nicola Blain, Victoria Hankin, Ben Huson Vlies, Nadia Lewis-Burke, Laura O-Neil, Rachel Powell, Jamie Rylance, Rebecca Tagney, Diane Wood, Dan Wootton
Belfast City Hospital	Peter Gray, Kathryn McDowell, Lorcan McGarvey (PI), Jolene Milligan, Brian Wells

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Bradford Royal Infirmary	Abid Aziz, Fahtima Begum, Stephen Cox, Umair Hamid, Rizwana Kausser, Leslie Masters, Sujie Mogane, Nabeela Nazir-Ahmed, Karen Regan, Dinesh Saralaya (PI), Kimberley Walker, Laura Walker, Helen Wilson
Queen's Hospital, Burton Hospitals NHS Foundation Trust	Ann Adams, Mosan Ashraf, Gillian Bell, Julie Birch, Elizabeth Kemp, Clare Mewies, Uttam Nanda (PI), Mandy Oakley, Alison Tilley, Louise Wilcox, Clare Williams
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Freeman Hospital, Newcastle	Nicholas Aitken, Angela Bailey, Marion Brooks, Jamie Brown, Gareth Davies, Jade Davison, Margaret Day, Anthony De Soyza (PI), Hazel Douglas, Maureen Foreman, Ben Hood, Rebecca Johnson, Gerry Jones, Karen Martin, Donna McEvoy, Yoko Okada, Jack Oliver, Leeanne Ratcliffe, Sarah Robertson, Therese Small, Graham Soulsby, Julie Stephenson, Hesther Wilson, Sarah Woolcock
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Raigmore Hospital, Inverness	Fiona Barrett, Jim Finlayson, Laura O'Keeffe, Debbie McDonald, Mary McKenzie, Lorna Murray (PI), Gordon Rushworth, Donna Patience
University Hospital Wishaw	Angela Brown, Craig Chalmers, Steven Marshall, Louise McGee, Donna Orr, Manish Patel, Fiona Ross, Andrew Smith (PI)
Royal Lancaster Infirmary	Mark Wilkinson (PI), Laura Booth, Jayne Craig, Jade Drew, Tim Gatheral, Rebecca Jeffery, Jane Ritchie, Vickie Rose, Andrew Taylor
Leighton Hospital, Crewe	Kelly Amor, Duncan Bailey, Christopher Brockelsby, Duncan Fullerton (PI), Nikki Gautam, Gareth Jones, Taya Jones, Syed Kazmi, Diana Lees, Emma Margerun, Julie Meir, Richard Miller, Andy Ritchings, Sarah Tinsley

Musgrove Park Hospital	James Allen, Korinna Andrews, Simon Barnes, Oliver Bintcliffe, Eliza Foster, Sarah Foster, Yvonne Moul, Justin Pepperell (PI), Dawn Redwood, Joy Rowe, Dinesh Shrikrishna, Tania Wainwright
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University Hospital of North Tees	Nicola Bateman, June Battram, Helen Carey, Julia Fuller, Richard Harrison (PI), Claire Irish, Graham Miller (PI), Lynda Poole, Ben Prudon, Angela Scott-Johnson, Gillian Wallace, Bill Wetherill
City Hospital, Nottingham	Tim Harrison (PI), Wendy Gerrard-Tarpey, Sheila Hodgson, Matthew Martin, Catherine Reynolds
Derriford Hospital, Plymouth	Julie Alderton, David Derry, Sharon Freeman, Jacinta Hardman, Maggie Kalita, Jennie Kingdon, Mike Marner, Tracy Mynes, Joanne Porter, Judy Sercombe, Caroline Snelgrove, Elizabeth Swanson, Trudy Turner, Neil Ward (PI), Jacqueline Westcott, Gloria Wong, Parag Yajnik
South Tyneside District Hospital	Amy Burns, Barrie Duncan, Nadia Elkaram, Liz Fuller (PI), Ben Hood, Paula Madgwick, Claire McBrearty, Sinead McHugh, Rachel Miller, Judith Moore, Asif Shah, Mark Shipley, Ruth Tindle, Michael Walton
Torbay Hospital	Gabrielle de Selincourt, Lee Dobson (PI), Lesley Evans, Bianca Hulance, Sally Maddison, Pauline Mercer, Sarah Mills, Andrew Mullinger, Hannah Shiels, Melanie Stone, Natalie Taylor, Christine Tsang, Amanda Vian, Sarah Wright
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Worcestershire Royal Hospital	Sarah Deacon, Alison Durie, Monica Gauntlett, Kim MacDonald, Terry Martin, Hugh Morrow, Stephen O'Hickey (PI), Heather Perry, Zee Shaan Parvez, Ann White

Yeovil District Hospital	Joanna Allison, Sarah Board, Clare Buckley, Sarah Debruijn, Dave Donaldson, Tracey Duckett, Adam Edwards, Alison Lewis, Tressy Pitt-Kerby, Rejendra Sinha (PI), Thikra Al Wattar (PI), Jodhi Wilson, Diane Wood
York Hospital, York Teaching Hospital NHS Foundation Trust	Andrew Atherton, Judith Bell, Claire Brookes, Poppy Cottrell, Cheryl Donne, Mark Elliot, Christopher Emms, Richard Evans, Caroline Everett, Mark R Fearnley, Monica Haritakis, Yvonne McGill, Heidi Redfearn, Davina Smith, Mandy Ward, Jacqueline Westmoreland, John White (PI), John Wightman, Paul Wood, Lorraine Wright
East of England primary care	
Alconbury & Brampton Surgeries	Melanie Fowler, Alyssa Lawford, Duncan Outram (PI), Caroline Ward
Alexandra & Crestview Surgeries	James Atkins (PI), Christina Easter, Barbara Stewart
Andaman Surgery	Jane Atkins, Mark Butt (PI), Sarah Butt, Hitesh Kumar, Sue Lock, Laverne Rose
Attleborough Surgeries	Sabrina Khalaque (PI), Ruth Mallinson, Lucy McLean, Paul Roebuck
Beccles Medical Centre	Kathleen Archer, Charlotte Hawkins (PI), Monica Kettlewell, Julia McLean, Sarah McLennan, Vasilica Munteanu, Charlene Wakefield
Bridge Road Surgery	Martin Aylward (PI), Carolyn Harper, Eleanor Schofield, Nicola Shea, Sue Vigus
Bridge Street Medical Centre (Cambridge)	Corinne Bakker (PI), Louise Norman
Bridge Street Surgery (Downham Market)	Clare Hambling (PI), Barbara Stewart, Megan Winterbone
Campingland Surgery	Mark Holmes (PI), Tracey Sharp, Maxine Smith, Liz Wing
Castle Partnership	Penny Atkinson, Richard Gilbert (PI), Jo Walsh
Coltishall Medical Practice	Alison Melton, Angela Norton, Rajesh Selvam, Michele Taylor, Neil Taylor (PI)
Comberton and Eversden Surgeries	Will Bailey, Janice Mills, Ian Parker (PI)
Cutlers Hill Surgery	Claire Craik (PI), Sarah Caplin, Daniel Treen
Davenport House	Jenny Hughes, Anthea Doran, Chas Thenuwara (PI)
De Parys Medical Centre	Carolyn Boyd, John Goudling (PI), Linda Lomax

East Norfolk Medical Practice	Liam Steven (PI), Lisa Matcalfe, Maxine Burton
Elizabeth Courtauld Surgery	Ali Alsawaf (PI), Sue Cole, Daniela Kreis-Alsayed, Phillipa Oval, David Sneddon, Jeanette Williams
Gorleston Medical Centre	Ann Abbott, Dawn Barnham, Lorraine Farrier, Sunder Gopaul (PI)
Greyfriars Medical Centre	Patrick Frew (PI), Katrina Kelly, Krystal Lewis-McDonald, Tara Maher, Stephanie Timberlake
Harvey Group Practice	Carolyn Downs, Matt Parfitt (PI)
Holt Medical Practice	Peter Franklin (PI), Annie Hughff
Hoveton & Wroxham Medical Centre	Carsten Dernedde (PI), Caroline Mansfield, Chris Wright
Linton Health Centre	Hayley Haworth, Laurence Kemp (PI), Claire Wade, Donna Watson, Fiona Wharton
Long Stratton Medical Partnership	Caroline Dear, Carol Gubby, Helen Mingaye, Mini Nelson (PI)
Ludham & Stalham Green Surgeries	Jessica Bane, Elizabeth Christie (PI), Tracey Edwards, Emma Lambon, Jennifer Liu
Mount Farm Surgery	Claire Giles (PI), Brian Ainsworth, Julie Friend, Peter Knights
Mundesley Medical Centre	Daryl Freeman (PI), Holly Fulcher, Carol Manson, India Mills, Jessica Payne
Nuffield Road Medical Centre	Tom Alderson (PI), Janette Bone, Jacqueline Day, Helen Jung, Sally Kaemer
Orchard Surgery, Dereham	Dawn Boyce, Stacey Hawkins, Jillian Pewtress, Vanaja Santosh (PI), Barbara Stewart
Peninsula Practice	Lindsey Crockett (PI), Linda Deabill, Ruth Osborne
Portmill Surgery	Jehad Aldegather (PI), Lynne Shoebottom
Rosedale Surgery	Amanda Ayers, Jodie Button, Maarten Derks (PI)
Roundwell Medical Centre	Chaminda Dooldeniya (PI), Tess Cantan, Denise Steward, Kirsti Withington
Salisbury House Surgery	Yasar Khan (PI), Mehar Singh (PI), Carol Bunting, Helen Ingle, Sally Szuca, Paul Vogwell (PI)
Sheringham Medical Practice	Pauline Craske, Susan Lees, Ian Smith (PI), Julie Sterry, Nikita Williamson
Spinney Surgery	Gill Avery, Reyny Rahman (PI), Debra Wheatley
St Stephens Gate Medical Practice	Frances Scouller (PI), Matthew Butler, Loraine Leggett

St Johns Surgery (Terrington)	Susan Atcheson (PI), Barbara Bruce, Jane Coston, Charlotte Walford
Staithe Surgery	Diana Hood (PI), Kate Bywater, Sylvia Jackson, Sue Perrott, Sally Ross-Benham
The Over Surgery	Lesley Bowring, Judith Davis (PI), Andrew Kennedy
Trinity & Bowthorpe Medical Practice	Gillian Denman, Xanthe Dunthorne, Helene Simper (PI)
Vida Healthcare	Ademola Adesanoya (PI), Felicity Bowerman, Audrey Brown, Janeen Henshaw, Lata Motwani, Amanda Pearson
Wells Health Centre	Gordon McAnsh (PI), Lisa Palmer, Jan Wright
Wellside Surgery	Jacqueline Martindale, Ian Williams (PI), Anita Willis
Woodhall Farm Medical Centre	David Adams, Winnie Chiu, Khalid Mirza (PI), Lucy Peppiatt
Woolpit Health Centre	Jenny Johnson, Karen Norcott, Ruth Osborne, William Smith, Richard West (PI)
Wymondham Medical Centre	Louanne Gault, Karen Hamer, Shelina Rajan, Stephen Thurston (PI)
York Street Medical Practice	Alistair Brown (PI), Helen Radlett, Stuart Thorpe
North of England Primary Care	
Beacon View Medical Centre	Vinod Kumar (PI), Alison McElvoy
Beaumont Park Medical Group	Jill Ducker, Angela McMenzie (PI)
Belford Medical Practice	Maureen Birdsall, Sebastian Moss (PI)
Bellingham Practice	Jill Ducker, Andrew Sewart (PI)
Benfield Park Medical Centre	Valerie Walker, Sian Williams (PI)
Burn Brae Medical Group	Anthea Adamson, Louise Chicken, Eleanor Gallagher, Nick Hargreaves (PI), Alison McClintock
Castlegate & Derwent Surgery	Jeanette Dixon, Mary Philipsz (PI), Barbara Robinson, Jackie Smith
Corbridge Medical Group	Janet Drinkwater, Jill Ducker, Sally Parkin (PI), Neil Stanley, Anna Townsend-Rose
Elvaston Road Surgery	Barbara Bailey, Stephen Hilton, Rachel Nixon
Fell Cottage Surgery	Rachel Nixon, Cheryl Rigg, Katherine Woodcock (PI)
Grove Medical Group	Alison Carlyle, Guy Clement (PI), Jill Ducker, Ann Hately, Cheryl Rigg, Hannah Smith

Guidepost Medical Group	Catherine Bromham (PI), Geraldine Richelle, Sue Rowlands, Geert Van Zon (PI)
Haltwhistle Medical Group	Sarah Davies (PI), Sarah Speed
Haydon Bridge & Allendale Medical Practice	Mary Douthwaite, Elaine Fiori, Emily Hadaway (PI), Mary Henderson
Hetton Group Practice	Julia Cook (PI), Jill Ducker, Judith Kirk, Rachel Nixon
Humshaugh & Wark Medical Group	Christine Counsell, Katherine Dixon, Louise Shearer, Hayley Wright (PI)
Marine Avenue Surgery	Ann Grieves, Justine Norman (PI)
Maryport Health Services	Ross Anderson (PI), Janice Cox, Jeanette Dixon, Janet Rasburn
Priory Medical Group	Andrew Duggan (PI), Jill Ducker, Tracey Pearson, Christine White
Prudhoe Medical Group	Michelle Orton, Margaret Ross, Helen Thornton (PI)
Seaton Park Medical Group	Aileen Rose, Emily Watson (PI)
Sele Medical Practice	Jill Ducker, Ben Frankel (PI), Julie Smith
Temple Sowerby Medical Practice	Jeanette Dixon, Helen Jervis (PI)
The Village Surgery	Jill Ducker, Simon Hartland, Linda Thompson (PI)
Waterloo Medical Group	Marie Imlach (PI), Elaine Sansom
West Farm Surgery	Christine Davidson, Kate Grisaffi (PI), Sally Morrison
South West England primary care	
Barton Surgery	Elizabeth Alborough (PI), Paula Brison, Ruth Christophers
Bovey Tracey & Chudleigh Practice	Carol Gubby, Rachael Minty, Daniel Thomas, Ben Ward (PI)
Brunel Medical Practice	Pamela Grills, Rayindra Naidoo, Lisa Van Kuyk, Richard Veale (PI)
Claremont Medical Practice	Kevin Douglas (PI), Beth Hawkes, Sonya McGill, Lucinda Ralph
Coleridge Medical Centre	Nigel De-Sousa (PI), Jane Stewart, Stacy Wilson
Helston Medical Centre	Gary Crocker, Linda Davies (PI), Linda Quinn
Ide Lane Surgery	Jackie Barrett, Jackie Crossman, Stephen Vercoe (PI), Rachel Winder
Petroc Group Practice	Philippa Haywood, Nicholas Jacobsen (PI), Alison Murton, Rebecca Nicholls, Martin Priest, Kirsty Rogers
Richmond House Surgery	Karen Bates (PI), Mary Guest, Sara McNamara, Kathy Polverino, Claire Southgate

Rolle Medical Partnership	Merilyn Green, Barbara Welch, William Willcock (PI)
Westlake Surgery	Jo Jones, Calli Smith, Lindsay Smith (PI)
Wessex primary care	
Friarsgate Practice	Tara Clark, Stephen Fowler (PI), Claire Hallett, Elaine Spellerberg
Park and St Francis Surgery	Amy Glanville, Natasha Campbell, Samuel Glanville, Jo King, Mark Rickenbach (PI), Clare Sharland
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APPENDIX 1: Rationale for the low-dose theophylline strategy

Population theophylline pharmacokinetic studies, during the 1970s and 80s have demonstrated that disease status, weight and smoking decreases the half life of theophylline and increases its clearance.[57-62] It has been shown that COPD patients who do not smoke have a reduced clearance compared to healthy volunteers.[60] Based on these data and our publications[63-66] an average population clearance value of theophylline in a non smoker is 40ml/hr/kg which is reduced to 32ml/hr/kg in a subject with COPD and by a further 20% if they have other related disease (eg severe congestive heart failure). This corresponds to the fast, normal and slow categories of plasma theophylline pharmacokinetic modelling, for COPD patients, provided in the table below. Smoking induces the theophylline clearance by approximately 60% which gradually returns to normal levels when they stop smoking. Other relevant population pharmacokinetic data, that is useful for loading doses, is a volume of distribution of 0.5L/kg.[57-66]

The use of actual weight or ideal body weight has been shown to have an effect on the clearance of theophylline in young adults that smoke. If a patient is obese they may be given a high dose when their actual weight is used. It is good practice to assume this occurs in all patients and thus use ideal body weight. Ideal body weight (IBW) can be calculated using the following equations.[67]

IBWfemale =45 + 0.9(height in cms-152) Kg
IBWmale = 50 + 0.9(height in cms-152) Kg

The ideal body weight is used unless the actual weight is lower than the ideal body weight.
For oral theophylline dosing the pharmacokinetic model is

$$\mathrm{Css} = \frac{\mathrm{F} \times \mathrm{D}}{\mathrm{Cl} \times \tau}$$

Where Css is the steady state theophylline concentration, F is the bioavailability of theophylline (F=1 for theophylline preparations), D is the dose, Cl is the clearance and τ is the dosage interval (either 12 or 24 hours). Using this model and the population theophylline clearance values for COPD patients, in smokers and non smokers, described above then predicted Css are a follows.

Table 33 The results of pharmacokinetic modelling for theophylline doses 200mg bd and od for current smoking/not- current smoking subjects by weight and theophylline clearance. The plasma theophylline concentrations using the dosing schedule are shaded. (Prof Henry Chrystyn, personal communication)

		Theophylline 200mg bd				Theophylline 200mg od		
		Steady state (Css) plasma theophylline concentration (mg/l)						
	Ideal body weight (kg)	Subject theophylline clearance				Subject theophylline clearance		
		Slow	Normal	Fast		Slow	Normal	Fast
Not current Smoker	40.1-50	17.4	13.0	10.4		8.7	6.5	5.2
	50.1-60	13.9	10.4	8.3		6.9	5.2	4.2
	60.1-70	11.6	8.7	6.9		5.8	4.3	3.5
	70.1-80	9.9	7.4	6.0		5.0	3.7	3.0
	80.1-90	8.7	6.5	5.2		4.3	3.3	2.6
	90.1-100	7.7	5.8	4.6		3.9	2.9	2.3
	100.1-110	6.9	5.2	4.2		3.5	2.6	2.1
	110.1-120	6.3	4.7	3.8		3.2	2.4	1.9
	>120	5.8	4.3	3.5		2.9	2.2	1.7
Current Smoker	40.1-50	10.9	8.1	6.5		5.4	4.1	3.3
	50.1-60	8.7	6.5	5.2		4.3	3.3	2.6
	60.1-70	7.2	5.4	4.3		3.6	2.7	2.2
	70.1-80	6.2	4.7	3.7		3.1	2.3	1.9
	80.1-90	5.4	4.1	3.3		2.7	2.0	1.6
	90.1-100	4.8	3.6	2.9		2.4	1.8	1.4
	100.1-110	4.3	3.3	2.6		2.2	1.5	1.2
	110.1-120	3.9	3.0	2.4		2.0	1.5	1.2
	>120	3.6	2.7	2.2		1.8	1.4	1.1

Confidence that low-dose theophylline can be achieved using the above dosing strategy is provided from a detailed analysis of a COPD study that measured theophylline concentrations for 3 different theophylline dosing regimens.[63] In 33 COPD patients (mean weight (SD) weight of 64.6(14.3) Kg and age of 61.2(5.8) years) we found that the mean (SD) plasma theophylline concentration at steady state when they received a mean of 252 (87) mg bd was 6.3 (2.1). This

represents a clearance value of 51.6 ml/hr/kg. When their dose was increased to 430mg bd and then to 597(153) bd their mean (SD) steady state plasma theophylline concentrations were 12.1(1.9) and 18.3(3.0) mg/L. This represents clearance values of 45.8ml/hr/kg and 42.1ml/hrkg. This will include smokers and non smokers (numbers of each not recorded) and the latter clearance value is similar to the 40ml/hr/kg used in the population pharmacokinetics modelling for the 'fast' category. Our other publications (n=83 patients);[64] (n=15)[65] patients) on plasma theophylline highlight our confidence of using low-dose theophylline in TWICS.

In the clinical situation whereby a clinician wishes to use intravenous aminophylline to treat a patient, participating in TWICS, with an acute exacerbation of COPD, the British National Formulary recommends a loading dose of intravenous aminophylline of 5mg/kg (typically 250mg), this is usually omitted if the patient is already taking theophylline, this is then followed by an intravenous infusion of aminophylline of 0.5mg/kg.[87] It is recommended that plasma theophylline be measured after 24 hours to direct the rate of further dosing. The pharmacokinetic model for a loading dose is

$$\mathrm{Co} = \frac{\mathrm{F} \times \mathrm{D}}{\mathrm{V}}$$

Where Co is the concentration immediately after the slow intravenous bolus dose of aminophylline, F is the bioavailability (F=0.8 for aminophylline) and V is the volume of distribution. A loading dose of 5mg/kg would provide a Co of

$$\mathrm{Co} = \frac{0.8 \times 5\mathrm{mg/kg}}{0.5\ \mathrm{L/kg}}$$
$$= 8\mathrm{mg/L}$$

Since the predicted Css shown in the table above ranges from 2.2 to 8.7 mg/L then the maximum theophylline comsentration would be 16.7 mg/L. Alternatively, a loading dose of 250mg aminophylline could be given rather than a dose based on weight. A loading dose of 250mg aminophylline in COPD patients weighing 40-100kg would provide a Co ranging from 10 to 4 mg/L. There is a linear relationship between Css and weight. Similarly if the loading dose was 500mg aminophylline then the predicted Css would be double that for the 250mg dose.

For an aminophylline infusion of 0.5mg/kg/hr.[87] Based on a clearance of 40ml/hr/kg and the

following pharmacokinetic model

$$\text{Css} = \frac{\text{F} \times \text{D}}{\text{Cl} \times \tau}.$$

[Where Css is the steady state theophylline concentration, F is the bioavailability of theophylline (F=0.8 for aminophylline preparations), D is the dose, Cl is the clearance (using a clearance of 40ml/hr/Kg) and τ is the dosage interval (1 hour for an intravenous infusion)] the predicted Css would be:

$$\text{Css} = \frac{0.8 \times 0.5\text{mg/hr/kg}}{0.04\text{L/hr/kg} \times 1} = 10\text{mg/L}.$$

Note that the predicted Css is irrespective of weight (see above equation). The predicted Css in a COPD non smoker classified with a slow, normal and fast theophylline clearance given an infusion of 0.5 mg/hr/kg would be 10. 12.5 and 16.7 mg/L. In a smoker the respective predicted Css be 6.3, 7.8 and 10.4 mg/L.

Importantly for the TWICS trial, it will be safe for participants to receive a 5mg/kg loading infusion of aminophylline followed by a 0.5mg/kg/hr infusion as the plasma concentration will not exceed the target 10-20mg/l range required for conventional theophylline dosing.

APPENDIX 2: Validation of patient reported exacerbations

Initially, we planned to validate the total number of COPD exacerbations for approximately 20% of participants by examination of GP records.

At the Trial Steering Committee meeting of 20 March 2017 the validation exercise comparing the number of exacerbations as recorded in GP records and reported by the participant was discussed. At that time, the focus of this validation had been in two of the largest sites: Aberdeen and Aintree. The validation was done by requesting a care/encounter summary from the GP and comparing this against patient report. In Aberdeen, 43 records had been checked; and in 37 there was complete agreement between patient report and GP report. In Aintree, 24 records had been checked and in 16 there was complete agreement between patient report and GP report. Therefore, 4% of participants had undergone validation, and there was approximately 80% concordance. Concerns were raised that there is no 'gold standard' for the reporting of exacerbations, and that current GP records may not be as reliable a source of exacerbation data as in the past, given that patients have rescue packs at home and can access help for their exacerbations through many non-GP sources, e.g. pharmacies, emergency and walk-in centres, Accident and Emergency Departments etc. The published evidence is that patients are able to reliably report the number of exacerbations experienced in the previous year,[112] furthermore the patient representatives for TWICS have been adamant that it is fairly straightforward to remember the number of exacerbations over this time-period. It was also noted that the primary outcome of this study is participant reported exacerbations and it is this outcome that drives demand for NHS services. The Trial Steering Committee therefore recommended that we completed the validation exercise for the participants we had data on; but that the validation exercise did not need to be extended beyond these two sites or to include further participants.

APPENDIX 3: Breaches

Site affected	*Description of breach*	*Assessment*
Site 36	The site consented a patient into the study on 28 April 2014 ***before*** the site agreement had been signed by all parties. The study processes in place prevented the site from randomising the patient on the live randomisation system and also meant that a drug pack could not be dispensed.	Non-serious
Site 18	Participant had rescue medication, including erythromycin (one of the drugs that can increase serum theophylline) and in response to an exacerbation, the participant started to take the rescue medication without stopping her study medication. The patient came to no harm, and did not suffer any adverse effects.	Non-serious
Site 11	The CI raised concerns about the monitoring process following a routine study monitoring visit carried out by R&D monitors at the site. For two patients, the monitors recorded amber findings relating to the recording of co-morbities and concomitant medication the case-report form, and for one patient indicated that there was contraindicated medication. However, the data recorded in both case report forms was accurate and both patients were eligible. The breach related to the monitors incorrectly noting amber findings and making the research nurses modify the case report form by entering incorrect information.	Non-serious
Site 12	Participant was admitted to hospital. Prior to the admission the participant had been prescribed clarithromycin (one of the drugs that can increase serum theophylline). His study medication was stopped by the hospital pharmacist. The symptoms experienced by the participant (gastro oesophageal reflux) may have resulted from clarithromycin per se, and/or an interaction between clarithromycin and theophylline. Gastro oesophageal reflux is a side effect of both clarithromycin and theophylline.	Non-serious

Site affected	*Description of breach*	*Assessment*
Site 11	The third party distributor identified that they had despatched a shipment to a participant which contained drug pack numbers 40167 (correctly) and 40166 (in error) on 5 November 2014. The participant was contacted on 29 January 2015 and indicated that he had started using kit number 40167 and that he had not opened kit number 40166. He returned kit number 40166 to the research nurse later that day and it was destroyed. The participant was resupplied with an appropriate box of medication.	Non-serious
Site 27	At the point of randomisation (20 April 2014) the participant had been randomised as a smoker (rather than as an ex-smoker) and was allocated and received a dose of twice daily study medication (he should have received a once daily dose). On 5 November 2014, the patient was diagnosed with Atrial Fibrillation. No palpitations were noted. Atrial tachycardias are a known side effect of theophylline. The patient was unblinded in order to manage appropriately. The atrial fibrillation experienced by the patient may have been caused by the theophylline. The participant was seen on 6 January 2015 for a routine appointment, and his pulse was noted to be regular, ie spontaneously reverted to sinus rhythm.	Serious
Site 12	Noted at 12 month follow-up the participant had been on Tildiem LA (300mg od) since recruitment into the study (26 February 2014). Tildiem LA is a form of diltiazem (diltiazem is one of the drugs listed into the trial protocol as known to interact with theophylline). Although this medication had been recorded on the baseline case report form, the patient was assessed as being eligible for the study. The patient was well throughout the study. No adverse events were noted.	Non-serious

Site affected	***Description of breach***	***Assessment***
Site 11	During the 12 month follow-up appointment (19 May 2015), the participant mentioned that the community pharmacist had been supplying Uniphyllin 200mg (theophylline) in his dosette box. After taking the Uniphyllin included in the dosette box for 2-3 days, the participant realised that he may be taking theophylline as both the TWICS study medication and as prescribed medication. He therefore ceased taking the TWICS study medication. The participant has noted no adverse effects as a result of this.	Non-serious

Site affected	*Description of breach*	*Assessment*
Site 78	Participant was randomised to twice daily study medication - dosing instruction "Take ONE tablet every morning and ONE tablet every evening" but took two tablets each morning and two each evening. After 10 days of taking the study medication, the participant noted he was experiencing nausea, tremors and disturbed sleep (which in part may have been anxiety related because of a forthcoming bypass operation); his dose was reduced by the study team to one tablet per day and his symptoms settled. At the six month follow-up appointment, the participant noted that they were still taking "one tablet" but as they were feeling well, wished to start taking two tablets again. The study team agreed that he could increase his dose to two tablets per day (the recommended "low-dose" dose for a smoker of his height and weight. He did this for three days and symptoms of nausea/sickness returned. The participant therefore reduced his dose to "one tablet" and the symptoms settled. In subsequent discussion with the participant it became clear that they had misinterpreted the initial instruction on medication use as two tablets twice day, and had been taking this dose rather than one tablet twice a day. For approximately 10 days between 3 December 2014 and 17 December 2014, he had therefore been taking a dose in the normal therapeutic range (400mg twice daily) rather than a low-dose (200mg twice daily). For the period between 17 December 2014 and 10 June 2015 he had been taking one tablet twice a day; this was the appropriate "low-dose" used within the study. For a further three days from 10 June 2015 the participant again misinterpreted the instruction on the medication bottle and took two tablets twice day (ie the normal therapeutic range rather than a low-dose).	Non serious

Site affected	*Description of breach*	*Assessment*
Site 12	Participant was prescribed Elleste Duet (which is an oestrogen; oestrogens may raise theophylline levels to within the normal therapeutic range rather than a low-dose) by her GP between being recruited into the study and her 6 month follow-up. At the six month follow-up (18 June 2015), she was advised to cease taking study medication. The interaction between Elleste Duet and theophylline is such that the serum levels of theophylline may be raised into the normal therapeutic range, and not to toxic levels. Thus any interaction does NOT raise safety concerns.	Non serious
Across sites	Following review of emergency hospital admissions captured at follow-up, we identified a number of admissions which should have been captured as SAEs. None related to study medication.	Non serious
Site 12	The participant failed to attend for 12 month follow-up. Follow-up data was sought from his GP, and during this data collection exercise, it was noted that the participant had been prescribed Uniphyllin on repeat prescription since 8 May 2012. He had not disclosed this at recruitment or 6 month follow-up, or during any telephone calls. The prescription he brought to the recruitment appointment did not include the Uniphyllin. No adverse events were noted during follow-up (last contact with participant was at the 46 week call).	Non serious
Site 12	Late reporting of an SAE in this participant (strangulated small bowel secondary to hernia, not related to study medication), who had ceased study medication prior to the event.	Non serious
Site 125	Participant was randomised on 12 January 2016 (200mg od); on 26 January it was noted that he was already taking Aminophylline (225mg bd). Patient had taken study medication as well as routine Aminophylline for 8 days. The patient did not experience any adverse reactions. The GP has confirmed that the Aminophylline (225mg bd) plus study medication (if active; 200mg od) would not have taken the participant over the maximum daily dose	Non serious

Site affected	*Description of breach*	*Assessment*
Site 12	The trial office prepared a waybill for the dispatch of study medication with the house number transposed (and so the study medication was delivered to house number 35 rather than house number 53). The participant was resupplied, and the incorrect delivery was retrieved from house number 35.	Non-serious
Site 78	The third party distributor picked the wrong kit and this was dispatched to the participant. The wrong kit was retrieved from the participant and she was resupplied with the correct kit.	Non-serious
Site 14	Participant was recruited into the TWICS study whilst participating in another drug study (in breach of the TWICS eligibility criteria). There was no documentation in the medical notes in relation to the other study and the patient did not mention it at recruitment. The patient came to no harm.	Non-serious
Site 145	Participant randomised on 23 June 2016 to once daily study medication, and was allocated an appropriate labelled bottle. The participant took study medication twice daily for approximately 7 days after commencing medication (this would have brought her into the normal therapeutic range for theophylline rather than a low-dose). The participant came to no harm (she noted some initial constipation which resolved).	Non-serious
Site 122	Participant was randomised to od study medication. The bottle was correctly labelled, but a dispensing label was added at the time the medication was dispensed which indicated a two a day dosing regimen. The error was noted and corrected. The participant took twice daily study medication for approximately 10 days (this would have brought him into the normal therapeutic range for theophylline rather than a low-dose) and came to no harm.	Non-serious

Site affected	*Description of breach*	*Assessment*
Site 159	In an attempt to prevent medication being prescribed that may interact with theophylline, the practice added theophylline to the repeat prescription as a study drug. The pharmacist dispensed liquid theophylline as part of the repeat prescription, and for a period of 7 days, the participant took a dose of liquid theophylline three times per day and also took their study medication three times per day. This would have brought the participant into the normal therapeutic range for theophylline rather than a low-dose. The participant came to no harm.	Non serious
Site 141	The third party distributor picked the wrong kit and this was dispatched to the participant. The wrong kit was retrieved from the participant and she was resupplied with the correct kit.	Non-serious
Site 115	Participant was recruited into the study in October 2015. During data checking in January 2017 it was noted that the participant was already taking Phyllocontin. The participant took trial medication for a full 12 months, and no adverse events were noted. Subsequent data checking identified five other participants who had been recruited whilst on a medication that may interact with theophylline: Site 32 – febuxostat; patient took study medication for 12 months, non-serious GI symptoms noted (abdominal pain, 2 x episodes of reflux) Site 80 – estradiol valerate; patient took study medication for 2 weeks and experienced non-serious side effects likely to be related to theophylline (nausea, headache, dizziness) Site 102 – roflumilast; participant took study medication for 12 months, no adverse reactions noted during 12 month follow-up Site 131 – elleste duet; participant continues of study medication (due to complete 12 month follow-up); no adverse reactions noted Site 131 – estradiol; participant continues of study medication (due to complete 12 month follow-up); no adverse reactions noted	Non-serious

APPENDIX 4: recruitment, by site

	Total number of participants recruited
Secondary care sites (n=33)	**1101**
Aberdeen Royal Infirmary	212
Aintree University Hospital NHS Foundation Trust	127
Belfast City Hospital	6
Queen Elizabeth Hospital Birmingham	54
Blackpool Victoria Hospital	57
Bradford Royal Infirmary	9
Queen's Hospital, Burton Hospitals NHS Foundation Trust	4
Calderdale Royal Hospital, Huddersfield Royal Infirmary, Calderdale & Huddersfield NHS Foundation Trust	4
University Hospital of North Durham	9
Lister Hospital, East and North Hertfordshire NHS Trust	20
Victoria Hospital, Kirkcaldy	29
Freeman Hospital, Newcastle	45
Glasgow Hospitals (Gartnavel, Glasgow Royal, Southern General, Victoria Infirmary, Western Infirmary)	115
Castle Hill Hospital, Hull	114
Raigmore Hospital, Inverness	31
University Hospital Wishaw	12
Royal Lancaster Infirmary	19
Leighton Hospital, Crewe	13
Musgrove Park Hospital	6
Norfolk and Norwich University Hospital	80
University Hospital of North Tees	6
City Hospital, Nottingham	11
Derriford Hospital, Plymouth	4
South Tyneside District Hospital	44
Torbay Hospital	12
New Cross Hospital, Wolverhampton	33
Worcestershire Royal Hospital	11
Yeovil District Hospital	8
York Hospital, York Teaching Hospital NHS Foundation Trust	6
East of England primary care (n=48)	**242**
Alconbury and Brampton Surgeries	6
Alexandra and Crestview Surgeries	5
Andaman Surgery	7
Attleborough Surgeries	7
Beccles Medical Centre	7
Bridge Road Surgery	4

	Total number of participants recruited
Bridge Street Medical Centre, Cambridge	2
Bridge Street Surgery, Downham Market	8
Campingland Surgery	2
Castle Partnership	8
Coltishall Medical Practice	4
Comberton and Eversden Surgeries	3
Cutlers Hill Surgery	2
Davenport House	3
De Parys Medical Centre	5
East Norfolk Medical Practice	1
Elizabeth Courtauld Surgery	1
Gorleston Medical Centre	3
Greyfriars Medical Centre	6
Harvey Group Practice	6
Holt Medical Practice	2
Hoveton and Wroxham Medical Centre	6
Linton Health Centre	5
Long Stratton Medical Partnership	4
Ludham & Stalham Green Surgeries	12
Mount Farm Surgery	3
Mundesley Medical Centre	14
Nuffield Road Medical Centre	4
Orchard Surgery, Dereham	3
Peninsula Practice	6
Portmill Surgery	4
Rosedale Surgery	3
Roundwell Medical Centre	5
Salisbury House Surgery	3
Sheringham Medical Practice	5
Spinney Surgery	4
St Stephens Gate Medical Practice	12
St.Johns Surgery, Terrington	5
Staithe Surgery	4
The Over Surgery	1
Trinity and Bowthorpe Medical Practice	2
Vida Healthcare	11
Wells Health Centre	3
Wellside Surgery	3
Woodhall Farm Medical Centre	3
Woolpit Health Centre	19

	Total number of participants recruited
Wymondham Medical Practice	1
York Street Medical Practice	5
North of England primary care (n=26)	**131**
Beacon View Medical Centre	8
Beaumont Park Medical Group	4
Belford Medical Practice	8
Bellingham Practice	1
Benfield Park Medical Centre	6
Burn Brae Medical Group	1
Castlegate & Derwent Surgery	29
Corbridge Medical Group	6
Elvaston Road Surgery	1
Fell Cottage Surgery	2
Grove Medical Group	1
Guidepost Medical Group	7
Haltwhistle Medical Group	2
Haydon and Allendale Medical Practice	1
Hetton Group Practice	4
Humshaugh and Wark Medical Group	3
Marine Avenue Surgery	2
Maryport Health Services	9
Priory Medical Group	2
Prudhoe Medical Group	4
Seaton Park Medical Group	2
Sele Medical Group	6
Temple Sowerby Medical Group	5
The Village Surgery	4
Waterloo Medical Group	11
West Farm Surgery	2
South West England primary care (n=11)	**95**
Barton Surgery	6
Bovey Tracey and Chudleigh Practice	9
Brunel Medical Practice	20
Claremont Medical Practice	4
Coleridge Medical Centre	3
Helston Medical Centre	2
Ide Lane Surgery	2
Petroc Group Practice	11
Richmond House Surgery	5
Rolle Medical Partnership	4

	Total number of participants recruited
Westlake Surgery	29
Wessex primary care (n=3)	9
Friarsgate Practice	1
Park and St Francis Surgery	1
Swanage Medical Centre	7
Total recruitment	1578

APPENDIX 5: Supplementary tables

Table 34: Baseline sociodemographic characteristics by location of recruitment

	Primary care (n = 917)			**Secondary care (N=619)**			**p-value**
Sex (N)	917			619			0.701
Male (n, %)		498	54.3		330	53.3	
Female (n, %)		419	45.7		289	46.7	
Age (N, Mean, SD)	917	68.9	8.2	619	67.7	8.5	0.006
Smoking status	917			619			<0.001
Current smoker (N, n, %)		322	35.1		164	26.5	
Ex-smoker (N, n, %)		595	64.9		455	73.5	
Pack years (N, Mean, SD)	910	46.1	29.5	619	48.4	27.1	0.113
BMI (N, Mean, SD)	917	27.4	6.1	619	27.0	6.1	0.284
BMI group	917			619			0.463
Underweight (N, n, %)		41	4.5		29	4.7	
Normal (N, n, %)		306	33.4		214	34.6	
Overweight (N, n, %)		296	32.3		214	36.6	
Obese (N, n, %)		274	29.9		162	26.2	

Table 34 (continued): Baseline clinical characteristics by location of recruitment

	Primary care			**Secondary care**			**p-value**
Exacerbations in the last 12 months (N, mean, SD)	908	3.35	1.8	619	3.92	2.5	<0.001
Exacerbations requiring hospitalisation in the last 12 months (N, mean, SD)	907	0.22	0.6	619	0.61	1.1	<0.001
GOLD 2011 category	901			615			0.006
C- ≥2 exacerbations in last year, mMRC 0-1 and CAT<10 (N, n, %)		60	6.7		21	3.4	
D ≥2 exacerbations in last year, mMRC ≥2and CAT≥10 (N, n, %)		841	93.3		594	96.6	
FEV_1 % predicted (N, mean, SD)	907	54.5	19.6	619	47.7	19.9	<0.001
FEV_1 % predicted category	907			619			<0.001
80+% [*GOLD mild*] (N, n, %)		100	11.0		40	6.5	
50-79.9% [*GOLD moderate*] (N, n, %)		399	44.0		207	33.4	
30-49.9% [*GOLD severe*] (N, n, %)		320	35.3		255	41.2	
0-29.9% [*GOLD very severe*] (N, n, %)		88	9.7		117	18.9	
FVC % predicted (N, mean, SD)	904	86.4	23.3	619	83.7	22.1	0.022
FEV_1/FVC ratio (N, mean, SD)	904	50.8	14.2	619	45.8	20.4	<0.001

Table 34 (continued): Baseline clinical characteristics by location of recruitment

	Primary care			Secondary care			p-value
Current treatment for COPD							
Inhaled Corticosteroid	917			619			0.001
ICS only (N, n, %)		26	2.8		5	0.8	
ICS LABA (N, n, %)		176	19.2		84	13.6	
ICS LAMA (N, n, %)		12	1.3		10	1.6	
ICS LABA/LAMA (N, n, %)		703	76.7		520	84.0	
Oral mucolytic use (N, n, %)	905	162	17.9	619	222	35.9	<0.001
Long-term antibiotic use (N, n, %)	905	34	3.8	619	62	10.0	<0.001
Co-morbidities							
Asthma (N, n, %)	905	186	20.6	618	93	15.1	0.006
Bronchiectasis (N, n, %)	905	22	2.4	617	43	7.0	<0.001
Ischaemic Heart Disease (N, n, %)	903	107	11.9	618	97	15.7	0.031
Hypertension (N, n, %)	905	351	38.8	618	231	37.4	0.579
Diabetes Mellitus (N, n, %)	905	102	11.3	618	72	11.7	0.819
Osteoporosis (N, n, %)	905	99	10.9	318	96	15.5	0.008
Anxiety/depression treated in last 5 years (N, n, %)	905	231	25.5	618	195	31.6	0.010
Cerebrovascular event (N, n, %)	905	58	6.4	619	45	7.3	0.511

BMI Body Mass Index, FEV_1 Forced expiratory volume in 1 second; FVC Forced vital capacity; GOLD Global Initiative for Chronic Obstructive Lung Disease, ICS Inhaled corticosteroid; IQR interquartile range, LABA Long acting β2 agonist; LAMA Long-acting muscarinic antagonists, SD standard deviation

Table 34: Baseline patient reported symptoms and quality of life by location of recruitment

	Primary care			**Secondary care**			**p-value**
Degree of breathlessness (mMRC dyspnoea)	907			617			<0.001
Not troubled by breathlessness except on strenuous exercise (N, n, %)		65	7.2		20	3.2	
Short of breath when hurrying or walking up a slight hill (N, n, %)		286	31.5		143	23.2	
Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace (N, n, %)		267	29.4		216	35.0	
Stops for breath after walking about 100 metres or after a few minutes on level ground (N, n, %)		234	25.8		186	30.2	
Too breathless to leave the house, or breathless when dressing or undressing (N, n, %)		55	6.1		52	8.4	
COPD assessment test (N, mean, SD)	905	21.6	7.6	615	23.9	7.6	<0.001
COPD assessment test group	905			615			<0.001
Low (score 0-9) (N, n, %)		60	6.6		21	3.4	
Medium (score 10-19) (N, n, %)		295	32.6		159	25.9	
High (score 20-29) (N, n, %)		391	43.2		285	46.3	
Very high (score 30-40) (N, n, %)		159	17.6		150	24.4	
EQ-5D-3L utility (N, mean, SD)	908	0.66	0.28	619	0.58	0.29	<0.001
EQ-5D-3L VAS (N, mean, SD)	907	61.7	19.3	617	59.1	18.9	<0.001

COPD Chronic Obstructive Pulmonary Disease, EQ-5D-3L EuroQoL 5 dimension 3 level, mMRC modified Medical Research Council, SD standard deviation, VAS visual analogue scale

Table 34: Baseline patient reported symptoms and quality of life by location of recruitment

	Primary care			***Secondary care***			***p-value***
Degree of breathlessness (mMRC dyspnoea)	*907*			*617*			*<0.001*
Not troubled by breathlessness except on strenuous exercise (N, n, %)		*65*	*7.2*		*20*	*3.2*	
Short of breath when hurrying or walking up a slight hill (N, n, %)		*286*	*31.5*		*143*	*23.2*	
Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace (N, n, %)		*267*	*29.4*		*216*	*35.0*	
Stops for breath after walking about 100 metres or after a few minutes on level ground (N, n, %)		*234*	*25.8*		*186*	*30.2*	
Too breathless to leave the house, or breathless when dressing or undressing (N, n, %)		*55*	*6.1*		*52*	*8.4*	
COPD assessment test *(N, mean, SD)*	*905*	*21.6*	*7.6*	*615*	*23.9*	*7.6*	*<0.001*
COPD assessment test group	*905*			*615*			*<0.001*
Low (score 0-9) (N, n, %)		*60*	*6.6*		*21*	*3.4*	
Medium (score 10-19) (N, n, %)		*295*	*32.6*		*159*	*25.9*	
High (score 20-29) (N, n, %)		*391*	*43.2*		*285*	*46.3*	
Very high (score 30-40) (N, n, %)		*159*	*17.6*		*150*	*24.4*	
EQ-5D-3L utility *(N, mean, SD)*	*908*	*0.66*	*0.28*	*619*	*0.58*	*0.29*	*<0.001*
EQ-5D-3L VAS *(N, mean, SD)*	*907*	*61.7*	*19.3*	*617*	*59.1*	*18.9*	*<0.001*

COPD Chronic Obstructive Pulmonary Disease, EQ-5D-3L EuroQoL 5 dimension 3 level, mMRC modified Medical Research Council, SD standard deviation, VAS visual analogue scale

Table 35: Baseline sociodemographic characteristics comparing those with and without HARQ data.

	HARQ not completed (N = 1134)			**HARQ completed (N = 402)**			**p-value**
Sex							
Male (N, n, %)	1134	629	55.5	402	199	49.5	0.039[a]
Age (N, Mean, SD)	1134	68.9	8.3	402	66.8	8.2	<0.001[a]
Smoking status	1134			402			0.396[a]
Current smoker (n, %)		352	31.0		134	33.3	
Ex-smoker (n, %)		782	69.0		268	66.7	
Pack years (N, Mean, SD)	1128	46.3	26.8	401	49.2	33.2	0.076[b]
BMI (N, Mean, SD)	1134	27.2	6.01	402	27.4	6.4	0.689[b]

[a] chi-squared test

[b] independent samples t-test

BMI Body Mass Index, SD Standard Deviation;

Table 36: Additional outcomes for ITT population for treatment of exacerbation

	Theophylline	Placebo	Model	Estimate	Lower CI	Upper CI	p-value
Exacerbations treated with antibiotics only							
Total number included in analysis	772	764					
Number with at least one exacerbation	230	227					
Total number of exacerbations	338	368					
Mean number of exacerbations	0.44	0.48	unadjusted IRR	0.94	0.78	1.13	0.484
SD (number of exacerbations)	0.82	0.97	adjusted IRR[a]	0.94	0.78	1.14	0.541
Exacerbations treated with steroids only							
Total number included in analysis	772	764					
Number with at least one exacerbation	77	88					
Total number of exacerbations	117	124					
Mean number of exacerbations	0.15	0.16	unadjusted IRR	0.93	0.66	1.32	0.697
SD (number of exacerbations)	0.60	0.58	adjusted IRR[a]	0.88	0.62	1.25	0.476
Exacerbations treated with antibiotics and steroids							
Total number included in analysis	772	764					
Number with at least one exacerbation	487	479					
Total number of exacerbations	1171	1106					
Mean number of exacerbations	1.52	1.45	unadjusted IRR	1.05	0.93	1.17	0.446
SD (number of exacerbations)	1.72	1.65	adjusted IRR[a]	1.02	0.92	1.14	0.725

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.

CI confidence interval, IRR incident rate ratio, HR hazard ratio, SD standard deviation

Table 37: Subgroup analysis for primary outcome (intention to treat analysis)

Category		Theophylline	Placebo	IRR[a]	Lower CI	Upper CI	Interaction p-value
All participants	N	772	764				
	Mean	2.24	2.23				
	SD	1.99	1.97	0.99	0.91	1.08	
Gender							
Male	N	418	410				
	Mean	2.23	2.18	1.01	0.87	1.17	
	SD	2.04	1.92				
Female	N	354	354				
	Mean	2.25	2.28	0.97	0.83	1.14	0.609
	SD	1.93	2.03				
Age group							
<60 years	N	115	131				
	Mean	2.33	2.46	0.91	0.70	1.19	
	SD	2.01	1.81				
60-69 years	N	313	284				
	Mean	2.27	2.13	1.07	0.89	1.28	0.198
	SD	2.06	1.81				
70+ years	N	344	349				
	Mean	2.18	2.23	0.96	0.82	1.13	0.637
	SD	1.92	2.01				
Smoking Status							
current	N	241	245				
	Mean	2.40	2.47	0.96	0.80	1.16	
	SD	2.01	2.07				
ex-smoker	N	531	519				
	Mean	2.16	2.11	1.01	0.89	1.16	0.561
	SD	1.97	1.92				
BMI category							
underweight	N	37	33				
	Mean	2.51	2.45	0.93	0.57	1.52	0.894
	SD	2.34	1.72				
normal	N	277	243				
	Mean	2.29	2.41	0.95	0.79	1.15	
	SD	1.91	1.72				
overweight/obese	N	458	488				
	Mean	2.18	2.13	1.02	0.88	1.17	0.478
	SD	2.01	1.96				

Table 37 (continued): Subgroup analysis for primary outcome (intention to treat analysis)

Category		Theophylline	Placebo	IRR	Lower CI	Upper CI	Interaction p-value
COPD treatment at baseline							
ICS/LAMA/LABA	N	610	613				
	Mean	2.33	2.36	0.98	0.87	1.10	
	SD	2.05	1.87				
ICS/LABA or ICS/LAMA	N	148	134				
	Mean	1.89	1.78	1.00	0.76	1.32	0.832
	SD	1.70	1.87				
ICS only	N	14	17				
	Mean	1.86	1.06	1.63	0.65	4.09	0.155
	SD	1.92	1.43				
Number exacerbations in 12 months prior to baseline							
2	N	286	308				
	Mean	1.61	1.53	1.05	0.86	1.28	
	SD	1.66	1.85				
3-4	N	317	298				
	Mean	2.31	2.25	1.02	0.86	1.21	0.785
	SD	1.93	1.85				
5+	N	169	158				
	Mean	3.16	3.55	0.89	0.73	1.09	0.139
	SD	2.21	2.38				
GOLD Stage							
I-II	N	370	376				
	Mean	1.93	2.03	0.97	0.82	1.14	
	SD	1.89	1.99				
III	N	286	289				
	Mean	2.38	2.40	1.02	0.85	1.21	0.605
	SD	2.03	1.99				
IV	N	113	92				
	Mean	2.90	2.58	0.99	0.75	1.32	0.849
	SD	2.03	2.04				
Oral corticosteroids at baseline							
no	N	418	410				
	Mean	2.23	2.18	0.99	0.88	1.10	
	SD	2.04	1.92				
yes	N	354	354				
	Mean	2.25	2.28	1.20	0.65	2.20	0.420
	SD	1.93	2.03				

Table 37 (continued): Subgroup analysis for primary outcome (intention to treat analysis)

Category		Theophylline	Placebo	IRR	Lower CI	Upper CI	Interaction p-value
ICS dose at baseline							
>=1600µg/day	N	549	547				
	Mean	2.38	2.31	0.98	0.87	1.12	0.642
	SD	1.98	2.03				
<1600µg/day	N	221	215				
	Mean	1.91	2.01	1.03	0.83	1.27	
	SD	1.98	1.80				

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
CI Confidence interval, SD Standard deviation, BMI Body mass index, GOLD Global Initiative for Chronic Obstructive Lung Disease, ICS Inhaled corticosteroid, IRR incidence rate ratio, LABA Long acting β2 agonist, LAMA Long acting muscarinic antagonist, µg microgram

Table 38: Sensitivity analysis for the ITT population excluding the 33 participants who died during 12 month follow-up- exacerbations and hospital admissions

	Theophylline	Placebo		Estimate	Lower CI	Upper CI	p-value
Total exacerbations							
Total number included in analysis	753	750					
Person years follow-up	738.6	735.1					
Number with at least one exacerbation	619	596					
Total number of exacerbations	1690	1678					
Mean number of exacerbations	2.24	2.24	unadjusted IRR	1.00	0.91	1.09	0.934
SD (number of exacerbations)	1.99	1.98	adjusted IRR[a]	0.99	0.91	1.07	0.729
Exacerbations requiring hospital treatment							
Total number included in analysis	753	750					
Person years follow-up	738.6	735.1					
Number with at least one exacerbation	99	118					
Total number of exacerbations	126	172					
Mean number of exacerbations	0.17	0.23	unadjusted IRR	0.73	0.55	0.97	0.032
SD (number of exacerbations)	0.49	0.66	adjusted IRR[a]	0.73	0.55	0.97	0.031
Non-COPD hospital admissions							
Total number included in analysis	744	741					
N with at least one	77	87					
Total number of admissions	111	111					
Mean admission rate	0.15	0.15	unadjusted IRR	0.99	0.71	1.38	0.949
SD admission rate	0.54	0.45	adjusted IRR[a]	1.03	0.74	1.43	0.875

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
CI confidence interval, COPD Chronic Obstructive Pulmonary Disease, IRR incident rate ratio, SD standard deviation

Table 39: Sensitivity analysis for the ITT population excluding the 33 participants who died during 12 month follow-up: lung function and patient reported outcomes

Outcome	Time point		Theophylline	Placebo		Overall mean difference	Lower CI	Upper CI	p-value
% Predicted FEV_1	Baseline	Total N	750	743					
		Mean	51.4	52.4					
		SD	20.0	19.8					
	6 months	Total N	548	535					
		Mean	52.4	53.2					
		SD	20.4	20.9					
	12 months	Total N	533	488					
		Mean	51.5	52.2	Unadjusted	-0.59	-2.54	1.36	0.551
		SD	20.4	21.6	Adjusted[a]	-0.58	-2.46	1.29	0.543
% Predicted FVC	Baseline	Total N	748	742					
		Mean	84.5	86.5					
		SD	22.2	23.5					
	6 months	Total N	543	531					
		Mean	84.0	84.6					
		SD	22.74	24.8					
	12 months	Total N	525	485					
		Mean	83.1	82.5	Unadjusted	-0.45	-2.59	1.69	0.678
		SD	23.8	25.1	Adjusted[a]	-0.37	-2.43	1.69	0.723

Table 39 (continued): Sensitivity analysis for the ITT population excluding the 33 participants who died during 12 month follow-up: lung function and patient reported outcomes

Outcome	Time point		Theophylline	Placebo		Overall mean difference	Lower CI	Upper CI	p-value
CAT score	Baseline	Total N	745	742					
		Mean	22.7	22.3					
		SD	7.6	7.9					
	6 months	Total N	668	653					
		Mean	21.2	21.1					
		SD	8.1	8.3					
	12 months	Total N	633	615					
		Mean	21.4	21.4	Unadjusted	0.16	-0.56	0.89	0.661
		SD	8.2	8.6	Adjusted[a]	0.02	-0.65	0.69	0.950
HARQ	Baseline	Total N	193	197					
		Mean	25.2	25.8					
		SD	16.1	14.9					
	6 months	Total N	189	187					
		Mean	21.9	22.8					
		SD	15.13	15.7					
	12 months	Total N	184	172					
		Mean	24.1	24.2	Unadjusted	-0.62	-3.15	1.91	0.631
		SD	15.70	15.94	Adjusted[a]	-0.89	-3.27	1.50	0.468

[a] adjusted for: centre (as a random effect), recruiting site (primary or secondary care), age centred on the mean, gender (male/female), smoking in pack years, FEV_1 % predicted, number of COPD exacerbations in the previous year, baseline COPD treatment, treatment with long term antibiotics.
CAT COPD Assessment Test, CI confidence interval, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, HARQ Hull Airways Reflux Questionnaire, SD standard deviation

APPENDIX 6: Line-listings of serious adverse events

Table 40: Events recorded as Suspected Unexpected Serious Adverse Reactions (SUSARs)

Case ID Country Gender Age	Event	Outcome	Date of onset Time to onset‡	Assessment of relatedness to study drug	Daily dose Route Formulation	Dates of treatment	Comments
System organ classification: Cardiac disorders							
ID 070 UK Female 72	2:1 AV block	Recovered with sequelae	April 2015	Possible	200mg theophylline once daily	4 March 2015 to 12 April 2015	*PI disputed diagnosis of AV block made by cardiology team. CI noted normal ECG after discontinuing study drug prior to development of AV block, also noted that theophylline increased heart rate rather than to slow it and therefore unlikely to be related to study drug.*
ID 143 UK Female 59	STEMI, PCI to LCx and OM, Cor Pulmonale, Mild to moderate LVSD on ventriculogram	Recovered	30 March 2016	Possible	200mg theophylline once daily	21 March 2016 to 27 March 2016	*PI suggested that there was possible association with study drug. CI noted that the participant had ceased study medication 3 days prior to the cardiac event and therefore highly unlikely to be related to study drug.*

Table 41: Events recorded as possible Serious Adverse Reactions (SARs)

Case ID†	Country Gender Age	Serious Adverse Event	Outcome	Date of onset Time to onset‡	Assessment of relatedness to study drug	Daily dose Route Formulation	Dates of treatment	Comments
System organ classification: Cardiac disorders								
007	UK Male 66	Atypical atrial flutter/atrial tachycardia	Recovered	25 August 2014	Possible	200mg theophylline twice daily	6 August 2014 to 12 August 2014; 19 August 2014 to 25 August	
018	UK Male 79	Syncopal episode resulting in fracture to right fourth metacarpal	Recovered	8 November 2014	Possible	200mg theophylline once daily	30 March 2014 to 31 March 2015	
029	UK Male 81	Atrial fibrillation	Not recovered	31 October 2014	Possible	200mg theophylline twice daily	30 April 2014 to 26 January 2015	
072	UK Male 82	Non-sustained ventricular tachycardia	Recovered with sequelae	14 August 2015	Possible	200mg theophylline once daily	25 August 2014 to 14 August 2015	
186	UK Male 76	Palpitations	Not recovered	11 August 2016	Possible	200mg placebo once daily	4 August 2016 – 11 August 2016	
189	UK Female 73	Palpitations and tachycardia	Not recovered	16 August 2016	Possible	200mg theophylline once daily	16 February 2016 – 5 September 2016	
213	UK Female 54	Palpitations	Unknown	12 October 2016	Probable	200mg placebo once daily	27 May 2016 – 17 October 2016	
233	UK Male 73	Sinus tachycardia	Recovered	18 November 2016	Possible	200mg placebo once daily	25 November 2015 ongoing at time of event	

Table 41 (continued): Events recorded as possible Serious Adverse Reactions (SARs)

Case ID†	Country Gender Age	Serious Adverse Event	Outcome	Date of onset Time to onset‡	Assessment of relatedness to study drug	Daily dose Route Formulation	Dates of treatment	Comments
System organ classification: Gastrointestinal disorders								
103	UK Female 71	Dyspeptic pain	Recovered	22 October 2015	Possible	200mg placebo once daily	12 October 2015 to 27 October 2015	
System organ classification: Investigations								
268	UK Male 76	Weight loss, lethargy	Unknown	19 April 2017	Possible	200mg placebo once daily	9 June 2016 ongoing at time of event	

Table 42: Events recorded as Serious Adverse Events (SAEs)a

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
System organ classification: Infections and infestations							
012	UK Male 74	Infected Elbow	Recovering	30 September 2014	200mg placebo once daily	12 September 2014 ongoing	
055	UK Female 54	Right leg cellulitis	Recovered	10 June 2015	200mg theophylline once daily	9 December 2014 to 11 December 2014	
060[b]	UK Female 82	Urinary tract infection	Unknown	9 July 2015	200mg placebo once daily	Never commenced study medication (study medication not dispensed)	*Did not start/initiate study medication*
071	UK Female 76	Sepsis	Recovered with sequelae	19 August 2015	200mg placebo once daily	1 July 2015 ongoing at time of event	
081	UK Male 70	Left arm cellulitis	Recovered	16 September 2015	200mg placebo once daily	3 April 2015 to 16 September 2015	
110	UK Female 75	Cellulitis lower leg secondary to cat bite	Unknown	13 December 2015	200mg theophylline once daily	2 December 2015 ongoing at time of event	
120	UK Female 77	Cellulitis, delirium	Recovered	13 December 2015	200mg theophylline once daily	13 February 2015 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
127	UK Female 82	Urinary tract infection	Recovered	29 December 2015	200mg theophylline once daily	27 February 2015 to 29 December 2015	
128	UK Female 71	Sepsis	Unknown	08 February 2016	200mg placebo once daily	26 January 2016 ongoing at time of event	
134	UK Male 79	Urinary tract infection and reduced mobility	Recovered	26 November 2015	200mg theophylline twice daily	16 September 2015 to 25 January 2016	
174	UK Female 64	Infection, ?source	Recovered	28 May 2016	200mg theophylline once daily	23 June 2015 ongoing at time of event	
181	UK, Female 76	Atrial flutter secondary to sepsis from lower limb cellulitis	Recovering	04 August 2016	200mg theophylline once daily	19 May 2016 ongoing at time of event	*Recorded as infection as this was the primary driver of atrial flutter*
201	UK Male 57	Exacerbation of COPD, leading to type 2 respiratory failure, bilateral leg swelling and also developed C. diff while in hospital	Unknown	13 June 2016	200mg placebo once daily	19 April 2016 to 13 July 2017	*Recorded as infection because of clostridium difficile infection. The exacerbation of COPD captured as primary outcome*
203	UK Female 78	Gram negative bacteraemia	Recovered	20 August 2016	200mg placebo once daily	15 July 2016 to 5 September 2016	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
217	UK Male 69	Cellulitis	Recovered	12 February 2015	200mg theophylline once daily	7 July 2014 to 24 November 2014	
220	UK Female 77	Infective gastroenteritis	Recovered	04 May 2016	200mg theophylline once daily	Never commenced study medication	*Did not start/initiate study medication*
221	UK Female 77	Cellulitis	Recovered	10 July 2016	200mg theophylline once daily	Never commenced study medication	*Did not start/initiate study medication*
222	UK Female 77	Confusion, possible secondary to cellulitis	Recovered	2 October 2016	200mg theophylline once daily	Never commenced study medication	*Did not start/initiate study medication* *Recorded as infection as this was the primary driver of confusion*
225	UK Male 78	Sepsis	Recovered	13 November 2016	200mg placebo once daily	14 June 2016 ongoing at time of event	
239	UK Male 74	Fall/?sepsis	Unknown	28 December 2016	200mg theophylline once daily	2 August 2016 ongoing at time of event	*Recorded as infection as this was the primary driver of falls*
244	UK Male 66	Ankle joint infection	Recovering	07 January 2017	200mg placebo once daily	22 January 2016 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
247	UK Female 65	Urinary tract infection	Recovered	10 October 2016	200mg placebo once daily	3 August 2016 ongoing at time of event	
249	UK Male 77	Urinary tract infection	Recovered	19 January 2017	200mg theophylline once daily	9 February 2016 ongoing at time of event	
251	UK Female 71	Periumbilical abscess	Recovered	6 October 2016	200mg theophylline once daily	27 November 2015 ongoing at time of event	
253	UK Female 60	Urinary tract infection and possible viral gastroenteritis	Recovered	10 December 2016	200mg theophylline once daily	21 March 2016 to 29 March 2016	
281	UK Male 71	Gastroenteritis	Recovered	6 February 2017	200mg theophylline once daily	9 June 2016 to 20 July 2016	
System organ classification: Neoplasm benign, malignant and unspecified							
010	UK Female 74	Moderately differentiated squamous cell carcinoma of supraglottic submucosal T3 N2c M0	Recovered	Unknown – reported 29 September 2014	200mg theophylline once daily	14 April 2014 to 28 February 2015	
011	UK Male 68	Lung cancer	Not recovered	Unknown Reported 30 September 2014	200mg placebo once daily	19 May 2014 to 30 September 2014	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
017	UK Female 71	Left lower lobe lesion with pleural effusion	Unknown	29 October 2014	200mg theophylline once daily	19 May 2014 to 13 November 2014	
019	UK Male 68	Metastatic lung cancer stage T2a N3 M1b	Fatal	18 November 2014	200mg theophylline once daily	7 July 2014 to 27 August 2014	
021	UK Female 85	Metastatic bladder cancer	Fatal	7 October 2014	200mg placebo once daily	2 April 2014 to 2 June 2014	
022	UK Male 70	Perforated caecal tumour	Fatal	24 November 2014	200mg theophylline once daily	24 July 2014 to November 2014	
039	UK Female 70	Intermediate grade neuroendocrine tumour/atypical carcinoid	Recovering	16 January 2015	200mg placebo once daily	7 March 2015 to 3 June 2015	
040	UK Female 77	Large pelvic mass/ Sigmoid carcinoma	Not recovered	12 April 2014	200mg theophylline once daily	21 May 2014 to 25 April 2015	
059	UK Female 79	Lung malignancy	Unknown	6 June 2015	200mg theophylline once daily	17 July 2014 to July 2015	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
068	UK Male 83	Lung cancer	Fatal	12 August 2015	200mg theophylline once daily	18 August 2014 to 27 May 2015	
078	UK Female 66	Metastatic colonic malignancy	Fatal	16 July 2015	200mg placebo once daily	16 December 2014 to 19 January 2015	
109	UK Male 63	Left breast cancer	Recovering	4 November 2015	200mg theophylline twice daily	24 June 2015 ongoing at time of event	
112	UK Male 61	Laryngeal cancer	Fatal	11 September 2015	200mg placebo once daily	Never commenced study medication	*Did not start/initiate study medication*
117	UK Female 64	Right hilar mass	Not recovered	15 December 2015	200mg theophylline once daily	5 August 2015 to 25 August 2015	
123	UK Male 80	Metastatic disease in the liver with no obvious primary	Unknown	11 December 2015	200mg placebo once daily	21 July 2015 to 31 August 2015	
132	UK Female 67	Central tumour, mediastinal lymphadenopathy, cerebral metastases	Not recovered	12 February 2016	200mg theophylline once daily	4 February 2016 to 19 February 2016	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
141	UK Male 67	Metastatic cancer	Unknown	17 March 2016	200mg placebo once daily	14 April 2015 to 13 April 2016	
147	UK Female 72	Lung cancer	Not recovered	1 April 2016	200mg theophylline once daily	15 October 2015 ongoing at time of event	
148	UK Female 72	Haemoptysis secondary to lung cancer	Recovering	1 April 2016	200mg theophylline once daily	15 October 2015 ongoing at time of event	
160	UK Female 76	Pancreatic malignancy with biliary obstruction	Fatal	3 May 2016	200mg theophylline once daily	17 March 2016 to 17 May 2016	
202	UK Male 61	T2 N2b squamous cell carcinoma of his right pyriform fossa	Unknown	8 March 2016	200mg placebo once daily	28 August 2015 ongoing at time of event	
219	UK Female 68	Lung neoplasm	Not recovered	Unknown	200mg theophylline once daily	19 July 2016 to 3 January 2017	
228	UK Female 59	Investigation following CT scan showing nodule - Primary lung tumour	Unknown	15 November 2016	200mg placebo once daily	1 June 2016 ongoing at time of event	
231	UK Male 70	Lung cancer	Not recovered	04 November 2016	200mg placebo twice daily	3 December 2015 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
238	UK Male 70	Grade 2 prostate cancer	Unknown	22 December 2016	200mg placebo once daily	28 July 2016 ongoing at time of event	
241	UK Female 58	Mastectomy for breast cancer	Recovering	19 December 2016	200mg theophylline once daily	18 February 2016 ongoing at time of event	
254	UK Female 67	Right breast cancer	Unknown	02 March 2017	200mg theophylline once daily	27 May 2016 ongoing at time of event	
260	UK Female 81	Uterine cancer	Recovering	27 February 2017	200mg theophylline once daily	3 March 2016 ongoing at time of event	
263	UK Female 64	Chronic lymphocytic leukaemia	Not recovered	5 April 2017	200mg placebo once daily	25 August 2016 ongoing at time of event	
286	UK Male 70	Hepatic flexure cancer (Dukes B)	Recovering	20 July 2017	200mg theophylline once daily	4 August 2016 ongoing at time of event	
289	UK Female 82	Death, I (a) Metastatic Cholangiocarcinoma, II COPD.	Fatal|	8 November 2017	200mg placebo once daily	Never commenced study medication	*Did not start/initiate study medication*
System organ classification: Blood and lymphatic system disorders							

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
173	UK Male 71	Iron deficiency anaemia	Recovered	18 February 2016	200mg placebo once daily	29 June 2015 ongoing at time of event	
184	UK Female 72	Abdominal haematoma	Recovering	03 May 2016	200mg placebo once daily	07 August 2015 ongoing at time of event	
System organ classification: Immune system disorders							
None							
System organ classification: Endocrine disorders							
None							
System organ classification: Metabolism and nutrition disorders							
245	UK Male 79	Dysphagia	Unknown	27 January 2017	200mg theophylline once daily	14 July 2016 to 31 January 2017	
246	UK Male 79	Refeeding syndrome	Unknown	28 January 2017	200mg theophylline once daily	14 July 2016 to 31 January 2017	
System organ classification: Psychiatric disorders							
073	UK Male 57	Overdose of amitriptyline and alcohol	Recovering	01 September 2015	200mg placebo once daily	04 August 2015 to 02 September 2015	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
098	UK Male 58	Overdose of amitriptyline and alcohol	Not recovered	8 November 2015	200mg placebo once daily	04 August 2015 to 02 September 2015	
146	UK Male 59	Admission to psychiatric ward with a depressive episode	Recovered	24 July 2015	200mg placebo twice daily	8 April 2015 to 30 June 2015	
183	UK Male 73	Asphyxiation as a result of suicide	Fatal	13 July 2016	200mg theophylline once daily	9 September 2015 to 13 July 2016	
System organ classification: Nervous system disorders							
014	UK Male 76	Transient ischaemic attack, atrial fibrillation	Recovered with sequelae	1 September 2014	200mg theophylline twice daily	3 June 2014 to 9 January 2015	
025	UK Male 76	Stroke	Recovering	11 November 2014	200mg theophylline twice daily	3 June 2014 to November 2014, restarted briefly at start of January 2015	
027	UK Male 66	Seizure secondary to intracerebral haemorrhage	Recovered	13 January 2015	200mg theophylline once daily	31 March 2014 to 26 March 2015	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
033	UK Female 44	Headache	Recovered	19 February 2015	200mg theophylline once daily	7 January 2015 ongoing at time of event	
043	UK Male 65	Subdural bleed/haematoma as result of fall prior to trial inclusion	Unknown	1 April 2015	200mg theophylline once daily	23 April 2015 ongoing at time of event	
050	UK Female 78	Suspected cerebral infarct	Recovering	23 May 2015	200mg placebo once daily	30 April 2015 to 21 May 2015	
064	UK Male 78	Subdural haemorrhage	Fatal	20 June 2015	200mg theophylline once daily	23 April 2015 to 23 July 2015	
077	UK Male 73	Spinal canal stenosis	Recovered	10 September 2015	200mg theophylline once daily	21 April 2015 to 9 September 2015	
080	UK Female 82	Partial anterior circulation infarct	Recovered	7 September 2015	200mg theophylline once daily	27 February 2015 to 7 September 2015	
085	UK Male 73	Chest pain / spinal stenosis	Recovered	20 July 2015	200mg theophylline once daily	13 October 2014 to 12 October 2015	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
099	UK Male 78	Lewy body dementia	Recovered	6 November 2015	200mg placebo once daily	1 December 2014 ongoing at time of event	
107	UK Female 82	Right total anterior circulation stroke syndrome or Todd's Palsy	Recovered	21 October 2015	200mg theophylline once daily	27 February 2015 ongoing at time of event	
114	UK Male 76	Bilateral thalamic infract	Not recovered	31 December 2015	200mg theophylline once daily	15 September 2015 ongoing at time of event	
118	UK Male 81	CVA	Recovering	31 December 2015	200mg placebo once daily	30 January 2015 then stopped trial drugs as soon as admitted.	
131	UK Female 58	?TIA	Recovering	18 January 2016	200mg placebo once daily	24 March 2015 to 18 August 2015	
140	UK Female 72	Dizziness and vomiting	Recovered with sequelae	22 March 2016	200mg theophylline once daily	01 April 2015 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
151	UK Male 62	Confusion with worsening headache	Recovered	16 December 2015	200mg placebo once daily	10 April 2015 to 15 April 2016	
172	UK Male 72	Ischaemic stroke, community acquired pneumonia	Recovering	1 July 2016	200mg theophylline once daily	2 February 2016 ongoing at time of event	
176	UK Female 79	Subarachnoid haemorrhage	Unknown	6 June 2016	200mg placebo once daily	15 September 2015 to 06 June 2016	
269	UK Male 68	Frontal lobe dementia	Fatal	Unknown	200mg placebo once daily	12 April 2016 to 18 October 2016	
System organ classification: Eye disorders							
None							
System organ classification: Ear and labyrinth disorders							
None							
System Organ Classification: Cardiac disorders							
004	UK Female 84	Pulmonary oedema	Recovered	24 June 2014	200mg placebo once daily	9 April 2014 to 20 June 2014	
013	UK Male 72	Death: Cause of death myocardial infarction, infective exacerbation of COPD, atrial fibrillation	Fatal	1 October 2014	200mg placebo once daily	30 May 2014 to 13 August 2014	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
026	UK Male 90	Orthostatic hypotension	Recovered with sequelae	28 December 2014	200mg theophylline once daily	7 May 2014 to 6 June 2014	
031	UK Male 75	Out of hospital cardiac arrest; end stage COPD; mitral valve prolapse	Fatal	8 January 2015	200mg theophylline once daily	21 June 2014 to 4 September 2014	
032	UK Male 57	Chest pain	Recovered	1 December 2014	200mg placebo once daily	31 March 2014 to 2 April 2015	
036	UK Male 71	Antero-lateral N-STEMI (myocardial infarction)	Recovered	26 February 2015	200mg placebo once daily	13 March 2014 to 26 February 2015	
042	UK Male 75	Cardiac arrest at home; Carcinoma of the right upper lobe and COPD	Fatal	28 April 2015	200mg placebo once daily	18 August 2014 to April 2015	
052	UK Female 76	Angina	Recovered with sequelae	11 July 2014	200mg theophylline once daily	3 April 2014 to 2 April 2015	
053	UK Female 76	Angina	Recovered with sequelae	31 July 2014	200mg theophylline once daily	3 April 2014 to 2 April 2015	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
056	UK Male 65	Atrial Fibrillation/flutter	Recovered with sequelae	16 June 2014	200mg placebo once daily	1 June 2015 to 16 June 2015	*Initially reported as possibly related to the study medication; at follow-up to the SAE reported as having no relationship to study medication.*
062	UK Female 78	Carotid vascular disease	Recovered with sequelae	4 June 2015	200mg placebo once daily	29 April 2015 to 12 May 2015	
063	UK Female 78	Angina	Recovered with sequelae	5 June 2015	200mg placebo once daily	29 April 2015 to 12 May 2015	
079	UK Female 82	Missed STEMI vs Broken heart syndrome	Recovered	16 August 2015	200mg theophylline once daily	27 February 2015 to 16 August 2015	
082	UK Female 70	Fast atrial fibrillation	Recovering	2 October 2015	200mg placebo once daily	25 November 2014 to 28 July 2015	
086	UK Male 59	Unstable angina	Recovered	09 September 2015	200mg placebo once daily	08 April 2015 to 30 June 2015	
097	UK Female 74	Left ventricular failure	Recovered	1 November 2015	200mg placebo once daily	6 January 2015 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
102	UK Male 82	Collapse not otherwise specified	Unknown	25 November 2015	200mg placebo once daily	21 May 2015 ongoing at time of event	
119	UK Female 77	Exacerbation of COPD; pulmonary congestion	Recovered	4 December 2015	200mg theophylline once daily	13 February 2015 ongoing at time of event	
122	UK Female 77	Left ventricular failure, secondary to acute MI, secondary sepsis, secondary to pneumonia	Fatal	17 January 2016	200mg theophylline once daily	14 February 2015 to 18 January 2016	*Recorded as cardiac because of pulmonary congestion, the exacerbation of COPD was captured as primary outcome*
126	UK Female 82	Congestive cardiac failure	Recovered	16 December 2015	200mg theophylline once daily	27 February 2015 to 16 December 2015	
133	UK Male 69	Cardiac arrest	Fatal	26 January 2016	200mg placebo once daily	21 October 2015 to 26 January 2016	
149	UK Female 62	Heart failure	Recovered	1 February 2016	200mg placebo once daily	14 April 2015 ongoing at time of event	
164	UK Male 79	Cardiac arrest	Fatal	12 May 2016	200mg theophylline once daily	31 October 2015 to 19 December 2015	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
178	UK Male 78	Heart failure, AKI	Fatal	21 July 2016	200mg theophylline once daily	01 June 2016 to 21 July 2016	
179	UK Male 68	Cardiac arrest	Fatal	9 July 2016	200mg theophylline once daily	27 November 2015 to 08 July 2016	
185	UK Male 76	?Heart attack	Not recovered	12 August 2016	200mg placebo once daily	3 June 2016 to 23 September 2016	
192	UK Female 64	Narrow complex tachycardia, exacerbation of COPD	Recovering	29 June 2016	200mg theophylline once daily	26 August 2015 ongoing at time of event	
195	UK Male 86	Chest pain – likely angina	Recovered	11 February 2015	200mg placebo once daily	5 September 2014 to 11 September 2014	
196	UK Male 86	Unstable angina	Recovered	09 June 2015	200mg placebo once daily	5 September 2014 to 11 September 2014	
205	UK Male 55	Acute Coronary Syndrome	Unknown	14 September 2016	200mg placebo twice daily	5 February 2016 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
223	UK Male 73	Acute myocardial infarction	Unknown	24 October 2016	200mg placebo once daily	7 June 2016 ongoing at time of event	
240	UK Female 78	Heart failure, moderate to severe AS	Unknown	29 November 2016	200mg placebo once daily	15 July 2016 to 5 September 2016	
242	UK Male 73	NSTEMI	Recovered with sequelae	15 October 2016	200mg theophylline once daily	1 February 2016 to 9 January 2017	
243	UK Male 63	Congestive heart failure	Recovering	21 December 2016	200mg placebo twice daily	26 July 2016 ongoing at time of event	
250	UK Female 69	ST elevation Myocardial Infarction	Recovered	23 February 2016	200mg placebo once daily	27 February 2015 to 30 July 2015	
258	UK Male 88	Non ST elevation myocardial infarction	Recovered	9 October 2016	200mg placebo once daily	13 November 2015 ongoing at time of event	
265	UK Male 64	End stage congestive cardiac failure	Fatal	12 April 2017	200mg placebo twice daily	26 July 2016 to 30 April 2017	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
276	UK Male 68	Acute Pulmonary Oedema	Fatal	1 June 2017	200mg theophylline once daily	14 July 2016 to 1 June 2017	
282	UK Female 65	Atrial Fibrillation and Heart Failure	Recovered	10 June 2016	200mg placebo once daily	11 May 2016 ongoing at time of event	
284	UK Female 69	Postural hypotension	Recovered	31 May 2017	200mg placebo once daily	11 August 2016 ongoing at time of event	
System Organ Classification: Vascular disorder							
001	UK Male 57	Old cerebellar gliosis/stroke	Recovered	25 April 2014	200mg placebo once daily	31 March 2014 ongoing at time of event	
066	UK Male 62	COPD with lower respiratory tract infection and DVT	Recovered	20 June 2015	200mg placebo once daily	18 September 2014 to October 2014 (18 doses in total)	*Recorded as vascular because exacerbation of COPD captured as primary outcome*
105	UK Male 75	Ruptured abdominal aortic aneurysm	Fatal	29 November 2015	200mg theophylline twice daily	14 October 2015 to 29 November 2015	
168	UK Female 76	Right leg DVT	Recovering	14 June 2016	200mg theophylline once daily	2 December 2015 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
182	UK Female 72	Collapse	Unknown	5 August 2016	200mg placebo once daily	26 January 2016 ongoing at time of event	
224	UK Male 78	Intracerebral haemorrhage	Recovered	6 November 2016	200mg placebo once daily	14 June 2016 ongoing at time of event	
252	UK Male 69	Right ICA occlusion	Recovering	26 December 2016	200mg placebo once daily	1 March 2016 to 17 February 2017	
255	UK Male 74	Bilateral subdural haematomas	Recovered with sequelae	28 December 2015	200mg theophylline once daily	21 April 2015 to 17 September 2015	
256	UK Male 74	DVT/PE	Recovered with sequelae	28 December 2015	200mg theophylline once daily	21 April 2015 to 17 September 2015	
267	UK Female 73	Uncontrolled hypertension	Recovered	13 April 2017	200mg theophylline once daily	13 April 2016 ongoing at time of event	
270	UK Male 68	Collapse ?cause	Recovered	17 June 2016	200mg placebo once daily	12 April 2016 to 18 October 2016	
285	UK Male 77	Ruptured abdominal aortic aneurysm	Fatal	7 August 2017	200mg theophylline once daily	17 August 2016 to 9 October 2016	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
System Organ Classification: Respiratory, thoracic and mediastinal disorders							
002	UK Male 70	Death – Pneumonia, diabetic hypoglycaemia	Fatal	12 May 2014	200mg theophylline once daily	24 April 2014 to 11 May 2014	
003	UK Female 74	pulmonary embolism	Recovered	24 June 2014	200mg placebo once daily	16 June 2014 ongoing at time of event	
015	UK Female 65	Death: exacerbation of COPD	Fatal	30 October 2014	200mg placebo once daily	24 June 2014 to 30 October 2014	
023	UK Female 69	Chest infection/chest pain/Left upper rib fracture	Recovered	17 October 2014	200mg placebo once daily	25 July 2014 to 29 July 2014	
024	UK Female 68	Death: type 2 respiratory failure, COPD, MS	Fatal	20 December 2014	200mg theophylline once daily	22 May 2014 to 27 August 2014	
034	UK Male 74	Death: severe COPD	Fatal	16 February 2015	200mg placebo once daily	16 June 2014 to February 2015	
035	UK Male 46	Hyperventilation	Recovered	11 November 2014	200mg placebo twice daily	10 September 2014 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
044	UK Male 73	Death: Exacerbation of COPD	Fatal	11 April 2015	200mg theophylline once daily	18 February 2015 to 7 April 2015	
046	UK Male 90	Symptomatic pleural effusions, hospital acquired pneumonia	Recovered with sequelae	11 May 2015	200mg theophylline once daily	7 May 2014 to 18 May 2015	
047	UK Male 47	Shortness of breath; most likely exacerbation of COPD	Recovered	6 December 2015	200mg placebo twice daily	10 September 2014 ongoing at time of event	
057	UK Female 73	Death: End stage COPD	Fatal	15 June 2015	200mg placebo once daily	3 March 2015 to 31 March 2015	
058	UK Female 74	Pleuritic chest pain	Recovered	15 March 2015	200mg theophylline once daily	10 July 2014 to 11 August 2014	
061	UK Male 72	Pleuritic chest pain	Recovered	20 July 2015	200mg theophylline once daily	10 July 2015 ongoing at time of event	
067	UK Male 62	Community acquired pneumonia, vomited, aspirated and cardiac arrest	Fatal	17 July 2015	200mg placebo once daily	18 September 2014 to October 2014 (18 doses in total)	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
069	UK Female 67	Pleuritic chest pain	Recovered	24 February 2015	200mg theophylline once daily	27 August 2014 to 09 November 2014	
083	UK Male 71	Increased breathlessness	Recovered	1 April 2015	200mg theophylline once daily	23 September 2014 to 12 October 2015	
088	UK Male 79	Cor Pulmonale secondary to COPD	Fatal	4 October 2015	200mg placebo once daily	21 April 2015 to 7 September 2015	
089	UK Male 83	Infective exacerbation of COPD, pleural effusion	Unknown	11 July 2015	200mg theophylline once daily	18 August 2014 to 27 May 2015	
093	UK Male 78	Shortness of breath	Recovering	09 October 2015	200mg placebo once daily	1 December 2014 ongoing at time of event	
116	UK Female 71	Pulmonary embolism	Recovering	19 December 2015	200mg placebo once daily	07 August 2015 ongoing at time of event	
124	UK Male 73	1a Acute kidney injury, 1b septicaemia, 1c lower respiratory tract infection; 2 COPD, AF, Acromegaly	Fatal	9 April 2015	200mg placebo once daily	1 May 2014 2015 to 08 April 2015	*Recorded as respiratory because prime driver was lower respiratory tract infection, acute kidney injury and septicaemia secondary.*

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
125	UK Male 80	Pneumonia	Fatal	31 December 2015	200mg placebo once daily	24 November 2015 to 30 December 2015	
154	UK Female 72	Pleuritic chest pain	Recovered	12 January 2016	200mg theophylline once daily	14 November 2015 to 20 December 2015	
155	UK Male 55	Renal failure, secondary to chest infection	Fatal	12 April 2016	200mg placebo twice daily	20 October 2015 to April 2016	*Recorded as respiratory because prime driver was lower respiratory tract infection, renal failure secondary*
165	UK Male 71	Haemoptysis	Recovered	11 May 2016	200mg placebo once daily	29 June 2015 ongoing at time of event	
166	UK Male 76	Bronchiectasis	Recovered	7 March 2016	200mg placebo once daily	10 December 2015 ongoing at time of event	
170	UK Male 72	Pneumothorax	Recovered	01 May 2016	200mg placebo once daily	8 July 2015 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
175	UK Female 64	Respiratory failure and CO narcosis following exacerbation of COPD and chest infection	Recovering	12 May 2016	200mg theophylline once daily	14 March 2016 to 12 May 2016	
177	UK Female 71	Pulmonary embolism	Recovering	18 July 2016	200mg theophylline once daily	28 November 2015 ongoing at time of event	
197	UK Male 70	Pneumonia, pulmonary embolism, cavitating lesion on CT chest	Recovered with sequelea	22 August 2016	200mg placebo once daily	4 May 2016 to 23 August 2016	
208	UK Male 63	Right pneumothorax	Recovered	27 June 2014	200mg theophylline once daily	24 April 2014 to 23 June 2014	
209	UK Male 63	Right pneumothorax	Recovered	31 August 2014	200mg theophylline once daily	24 April 2014 to 23 June 2014	
212	UK Female 64	Pleurisy or musculoskeletal pain	Recovered	10 February 2016	200mg theophylline once daily	09 April 2015 ongoing at time of event	
226	UK Female 59	Bronchiectasis	Unknown	15 November 2016	200mg placebo once daily	1 June 2016 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
230	UK Female 55	Hypoxia	Recovering	28 November 2016	200mg placebo once daily	20 January 2016 ongoing at time of event	
234	UK Male 62	COPD	Fatal	Unknown	200mg theophylline once daily	19 January 2016 ongoing at time of event	
248	UK Male 79	Aspiration pneumonia	Fatal	02 February 2017	200mg theophylline once daily	14 July 2016 to 31 January 2017	
257	UK Male 88	Chest infection	Fatal	20 February 2017	200mg theophylline once daily	6 March 2016 to 25 February 2017	
264	UK Male 68	1) bilateral bronchopneumonia 2) pulmonary oedema secondary to heart failure and acute kidney injury 3) progressive frontal lobe dementia and COPD	Fatal	22 November 2016	200mg placebo once daily	12 April 2016 to 18 October 2016	
266	UK Female 71	Pleuritic chest pain	Recovered	12 July 2015	200mg placebo once daily	15 September 2014 to 2 February 2015	
288	UK Female 78	Death, pneumonia, severe COPD, frailty	Fatal	9 December 2015	200mg theophylline once daily	20 April 2015 to 17 November 2015	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
System organ classification: Gastrointestinal disorders							
009	UK Male 55	Adhesional Bowel Obstruction	Recovered	11 September 2014	200mg theophylline once daily	24 May 2014 to 11 September 2014	
016	UK Male 76	Blockage in oesophagus	Recovered	1 November 2014	200mg theophylline once daily	2 October 2014 ongoing at time of event	
020	UK Male 72	Inflammation of oesophagus	Recovered	16 September 2014	200mg placebo once daily	8 July 2014 to 24 June 2015	
030	UK Female 82	Viral gastroenteritis	Recovered	15 January 2015	200mg placebo once daily	1 April 2014 to January 2015	
037	UK Female 43	Abdominal pain and liver steatosis	Unknown	11 March 2015	200mg theophylline once daily	13 January 2015 ongoing at time of event	
038	UK Female 79	Vomiting, fever, severe abdominal pain	Recovering	21 March 2015	200mg placebo once daily	4 February 2015 to 8 August 2015	
048	UK Male 78	Diverticulitis	Recovered	8 September 2014	200mg placebo once daily	6 March 2014 to 15 October 2014	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
049	UK Male 78	Diverticulitis	Recovered	8 December 2014	200mg placebo once daily	6 March 2014 to 15 October 2014	
051	UK Female 72	Severe constipation	Recovered	7 June 2015	200mg theophylline once daily	2 May 2014 to 5 May 2014	
054	UK Female 54	Gastritis	Recovered	25 April 2015	200mg theophylline once daily	9 December 2014 to 11 December 2014	
065	UK Female 58	Diverticulitis	Recovered	26 July 2015	200mg placebo once daily	3 July 2015 ongoing at time of event	
074	UK Male 66	Appendicitis	Recovered	28 August 2015	200mg theophylline once daily	29 July 2015 to 27 August 2015	
087	UK Male 71	Laparoscopic appendectomy	Recovered	09 November 2014	200mg theophylline once daily	05 September 2014 ongoing at time of event	
090	UK Female 82	Abdominal pain	Recovered	5 October 2014	200mg theophylline once daily	14 May 2014 to 17 May 2014	
100	UK Female 59	Strangulated small bowel secondary to hernia	Recovered	1 November 2014	200mg placebo once daily	4 August 2014 to 1 September 2014	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
101	UK Female 60	Oesophagitis and oesophageal stricture	Recovered	6 July 2015	200mg placebo once daily	4 August 2014 to 1 September 2014	
111	UK Male 71	Haematemesis	Recovered	22 November 2014	200mg placebo once daily	20 March 2014 ongoing at time of event	
121	UK Male 58	Perforated duodenal ulcer	Recovered	25 September 2015	200mg theophylline once daily	03 February 2015 to 15 January 2016	
129	UK Male 49	Laparotomy and adhesiolysis following severe abdominal pain.	Recovering	15 February 2016	200mg theophylline twice daily	23 April 2015 ongoing at time of event	
136	UK Male 70	Rectal bleed. ? Infective/ ischaemic colitis	Recovering	6 March 2016	200mg theophylline once daily	12 August 2015 to 31 December 2015	
150	UK Male 71	Diverticular disease	Recovered	6 April 2016	200mg theophylline once daily	22 March 2016 ongoing at time of event	
158	UK Female 72	Nausea and vomiting, acute abdominal pain	Recovering	3 May 2016	200mg theophylline once daily	26 November 2015 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
163	UK Male 56	Anal abscess/fistula	Not recovered	10 January 2016	200mg theophylline twice daily	04 July 2015 ongoing at time of event	
171	UK Male 71	Diverticulitis	Unknown	27 June 2016	200mg theophylline once daily	21 March 2016 to 29 June 2016	
193	UK Male 59	Bowel obstruction	Recovered	05 August 2016	200mg theophylline once daily	29 July 2016 ongoing at time of event	
198	UK Female 59	Gastroenteritis	Recovered	01 May 2016	200mg theophylline once daily	21 March 2016 to 29 March 2016	
210	UK Female 71	Acute pancreatitis	Recovering	6 October 2016	200mg theophylline once daily	27 November 2015 ongoing at time of event	
235	UK Male 68	(COPD) and acute upper gastro intestinal haemorrhage due to duodenal ulcer	Fatal	Unknown	200mg theophylline twice daily	28 June 2016 to 19 December 2016	*Recorded as gastrointestinal because exacerbation of COPD captured as primary outcome*
262	UK Male 80	Constipation	Recovered with sequelae	05 March 2017	200mg placebo once daily	11 May 2016 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
275	UK Female 88	Constipation	Recovered	06 December 2016	200mg placebo once daily	1 June 2016 ongoing at time of event	
277	UK Male 76	Constipation	Recovered	28 December 2016	200mg theophylline once daily	3 June 2016 to 22 June 2016	
279	UK Female 73	Diverticulitis 'flare up'	Recovered	02 March 2017	200mg theophylline once daily	18 July 2016 to 2 August 2016	
287	UK Male 77	Constipation	Unknown	8 May 2017	200mg theophylline once daily	17 August 2016 to 9 October 2016	
System organ classification: Hepatobiliary disorders							
008	UK Male 66	Acute hepatitis	Recovered	25 August 2014	200mg placebo twice daily	23 August 2014 to 25 August 2014	
130	UK Female 67	Obstructive jaundiced and evidence of intraductal calculi	Recovered	11 January 2016	200mg placebo once daily	24 February 2015 ongoing at time of event	
138	UK Female 68	Vomiting	Recovered	22 November 2015	200mg theophylline once daily	20 March 2015 to 11 March 2016	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
152	UK Female 72	Cholangitis and laparoscopic cholecystectomy	Recovered	21 December 2015	200mg theophylline once daily	14 November 2015 to 20 December 2015	
236	UK Male 76	Groin pain (possible biliary sepsis)	Recovered	12 August 2016	200mg placebo once daily	7 June 2016 ongoing at time of event	
273	UK Male 87	Gallstones	Recovered with sequelae	1 November 2016	200mg placebo once daily	24 August 2016 ongoing at time of event	
System organ classification: Skin and subcutaneous tissue disorders							
135	UK Male 80	Skin rash	Recovered	29 December 2015	200mg theophylline once daily	February 2015 to 14 February 2015	
System Organ Classification: musculoskeletal and connective tissue disorders							
006	UK Male 61	Suspected fractured ribs	Recovering	31 May 2014	200mg placebo once daily	4 March 2014 to 10 May 2014	
084	UK Female 55	Chest pain	Recovered	3 July 2015	200mg placebo once daily	24 April 2015 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
092	UK Female 58	Atypical chest pain	Recovered	27 August 2015	200mg placebo once daily	11 May 2015 ongoing at time of event	
139	UK Female 69	Chest tightness	Recovered	11 January 2016	200mg theophylline once daily	23 September 2015 ongoing at time of event	
144	UK Male 82	Acute stiff neck	Recovering	25 February 2016	200mg placebo twice daily	21 May 2015 to 25 February 2016	
145	UK Male 82	GP referral due to swallowing problems and neck pain ongoing at time of event for 2-3 weeks	Recovered with sequelae	21 March 2016	200mg placebo twice daily	21 May 2015 to 25 February 2016	
156	UK Female 72	Left rib fracture (osteoporotic, not traumatic)	Recovering	25 April 2016	200mg placebo once daily	7 August 2015 ongoing at time of event	
159	UK Male 71	Musculoskeletal chest pain	Recovering	10 May 2016	200mg theophylline once daily	17 November 2015 to 17 May 2016	
161	UK Male 56	Hyperaesthesia of insulin injection site	Recovered	11 December 2015	200mg placebo once daily	25 June 2015 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
162	UK Male 56	Right ankle pain, ?cellulitis	Recovering	3 May 2016	200mg placebo once daily	25 June 2015 ongoing at time of event	
187	UK Male 61	Musculoskeletal chest pain	Recovered	3 May 2014	200mg theophylline once daily	24 April 2014 to 23 June 2014	
188	UK Male 71	Chest pain	Recovered	16 August 2016	200mg placebo once daily	17 November 2015 ongoing at time of event	
199	UK Female 59	Musculoskeletal pain	Recovered	03 July 2016	200mg theophylline once daily	21 March 2016 to 29 March 2016	
211	UK Female 76	Back pain following fall	Recovered	14 May 2015	200mg placebo once daily	5 June 2014 to 9 June 2014	
259	UK Female 72	Primary diagnosis gout of her Left big toe, with a secondary diagnosis of infection	Unknown	1 March 2017	200mg theophylline once daily	18 April 2016 ongoing at time of event	
261	UK Female 76	Abdominal pain	Recovered	01 February 2017	200mg placebo once daily	26 August 2016 ongoing at time of event	*Considered to be of musculoskeletal origin*
System organ classification: Renal and urinary disorders							

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
076	UK Male 60	Kidney stones	Recovering	2 September 2015	200mg placebo once daily	6 January 2015 ongoing at time of event	
104	UK Male 83	Urinary retention	Recovering	18 November 2015	200mg placebo once daily	28 May 2015 ongoing at time of event	
106	UK Female 82	Acute kidney injury	Recovered	30 November 2015	200mg theophylline once daily	27 February 2015 ongoing at time of event	
157	UK Male 63	Right renal colic	Recovered	29 Feb 2016	200mg placebo twice daily	04 November 2015 to 05 January 2016	
200	UK Female 59	UTI with stage 1 AKI	Recovered	16 August 2016	200mg theophylline once daily	21 March 2016 to 29 March 2016	
207	UK Female 75	Multi-resistant E.coli UTI	Recovered	25 November 2014	200mg theophylline once daily	28 August 2014 to 1 September 2014	
229	UK Female 73	Deranged renal function, lower respiratory tract infection,	Recovered	20 November 2016	200mg theophylline once daily	11 April 2016 to 20 April 2016	
237	UK Male 76	Haematuria	Recovering	2 December 2016	200mg placebo once daily	7 June 2016 to 12 August 2016	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
280	UK Male 83	Shortness of breath due to fluid overload secondary to renal disease	Recovered	30 March 2016	200mg theophylline once daily	2 March 2016 to 12 April 2016	
283	UK Female 78	Proximal ureteric stone causing obstruction of left kidney.	Recovered	5 December 2016	200mg theophylline once daily	26 July 2016 ongoing at time of event	
System Organ Classification: Pregnancy, puerperium and perinatal conditions							
None							
System Organ Classification: Reproductive system and breast disorders							
None							
System Organ Classification: Congenital, familial and genetic disorders							
None							
System Organ Classification: General disorders and administration site conditions							
None							
System organ classification: Investigations							
113	UK Female 55	Asymptomatic raised calcium levels	Recovered	4 December 2015	200mg placebo once daily	23 June 2015 ongoing at time of event	
System Organ Classification: Injury, poisoning and procedural complications							

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
005	UK Female 68	Left tibial plateau fracture	Recovering	1 July 2014	200mg theophylline once daily	8 May 2014 ongoing at time of event	
028	UK Female 67	Fractured pubic ramus and right acetabulum	Recovered	12 November 2014	200mg theophylline once daily	22 August 2014 to 9 November 2014	
041	UK Male 55	Death: Head Injury	Fatal	19 April 2015	200mg theophylline once daily	13 March 2015 to 19 April 2015	
075	UK Male 90	Fall (mechanical)	Recovered	12 March 2015	200mg placebo once daily	4 September 2014 to September 2015	
091	UK Female 58	Rectus sheath haematoma	Recovered	23 September 2015	200mg placebo once daily	11 May 2015 ongoing at time of event	*Secondary to trauma*
094	UK Male 85	Fractured neck of femur	Recovered	14 August 2015	200mg placebo once daily	23 March 2015 ongoing at time of event	
095	UK Female 82	Fracture left wrist	Recovered	28 April 2015	200mg placebo once daily	30 October 2014 to 5 November 2014	
096	UK Female 65	Fractured distal radius and ulna	Recovered	04 September 2015	200mg placebo once daily	15 June 2015 ongoing at time of event	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
108	UK Male 49	Laceration to left hand	Unknown	29 September 2015	200mg theophylline twice daily	23 April 2015 ongoing at time of event	
115	UK Female 76	Fall	Recovered	26 December 2015	200mg placebo once daily	12 December 2015 to 31 December 2015	
137	UK Male 60	Lower back pain since fall on floor during the night for 2 hours duration	Recovered	7 March 2016	200mg theophylline once daily	7 April 2015 ongoing at time of event	
153	UK Female 72	Post-op wound infection	Recovered	9 January 2016	200mg theophylline once daily	13 November 2015 to 20 December 2015	
169	UK Male 80	Raised INR 4.2 and HB 97; ?GI bleed	Recovering	01 July 2016	200mg theophylline once daily	21 October 2015 ongoing at time of event	*Inappropriately high dose of warfarin*
180	UK Male 83	Head injury	Recovered	06 July 2016	200mg placebo once daily	10 February 2016 ongoing at time of event	
190	UK Male 69	Fractured rib	Not recovered	19 August 2016	200mg placebo once daily	21 March 2016 ongoing at time of event	
204	UK Female 81	Right distal fibula and medial malleolus	Unknown	03 September 2016	200mg theophylline once daily	19 July 2016 to 19 December 2016	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
206	UK Male 74	Fell downstairs and fractured clavicle, shoulder and broke ribs	Recovering	1 August 2016	200mg placebo once daily	24 August 2015 to 11 February 2016	
214	UK Male 63	Fall	Recovered	15 January 2015	200mg placebo once daily	4 March 2014 ongoing at time of event	
216	UK Male 69	Persistent vomiting	Recovered	17 January 2015	200mg theophylline once daily	7 July 2014 to 24 November 2014	*Thought to be related to chemotherapy*
218	UK Male 69	Confusion (steroid induced psychosis)	Recovered	04 April 2015	200mg theophylline once daily	7 July 2014 to 24 November 2014	
271	UK Female 76	Closed fracture neck of femur	Unknown	14 May 2017	200mg placebo once daily	27 May 2016 ongoing at time of event	
272	UK Male 58	Fall like syncopal attack	Recovered	26 March 2015	200mg theophylline once daily	12 March 2015 to 18 April 2015	
274	UK Male 84	Fall	Fatal	14 October 2016	200mg placebo once daily	23 May 2016 to 6 October 2016	

Case ID	*Country* *Gender* *Age*	*Serious Adverse Event*	*Outcome*	*Date of onset* *Time to onset‡*	*Daily dose Route* *Formulation*	*Dates of treatment*	*Comments*
278	UK Female 61	Fractured neck of femur	Recovered	8 May 2017	200mg placebo once daily	17 May 2016 ongoing at time of event	
System organ classification: Surgical and medical procedures							
045	UK Male 69	Optical urethrotomy	Recovered	27 March 2015	200mg theophylline twice daily	30 July 2014 to 29 July 2015	
System organ classification: Social circumstances							
None							

[a] Seven other events were recorded by sites as SAEs. These are not reported in the tables above (or in table 16 in the main body of the report) for the following reasons: Two were retracted because they were not considered to be serious (IDs 167, 191); One was retracted and resubmitted as a follow-up (ID 194); Four captured primary (COPD exacerbation) or secondary (pneumonia) outcome data and are reported as such in chapter 4 (IDs 142, 215, 227 and 232)

[b] Event not included in Table 16 as this person did not start their study medication